Conceptual design of a microfluidic-based platform for medical diagnosis

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Bachelor Thesis Industrial Design Engineering

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Benchmark

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Glossary

ELISA	Enzyme-linked immunosorbent assay; commonly used medical assay to detect proteins using antibodies directed at the protein to be measured
Genome	Genetic material of an organism
Hematology	Branch of medicine concerned with the blood
Immonodiagnostics	Diagnostics based on immunoassays
Immunoassay	Biochemical test that measures the presence of a molecules in a solution using antibodies or antigens
Molecular diagnostics	Analysis of biological markers in the genome
Monoplex test	Test capable to assess a single variable
Multiplex test	Test capable to assess multiple (complex) variables
Pathogenomics	Bacteria, virus, or microorganism that can cause disease
Pathogenomics	Genomic research on pathogens
Reagent	A substance or mixture for use in chemical analysis or other reactions
Renal dysfunction	Kidney failure
Spectrophotometer	Optical instrument for measuring the intensity of light relative to wavelength
Spectroradiometer	Optical instrument for measuring wavelength and amplitude of light

Abbreviations

CAD	Computer aided design
CLIA	Clinical Laboratory Improved Amendments
DNA	Deoxyribonucleic acid
EMS	Engineering and Manufacturing Services
GP	General practitioner
GUI	Graphical user interface; look and feel of software
HTS	High-throughput screening
ICU	Intensive care unit
LOC	Lab-on-a-chip
MS	Mass spectrometry
NAAT	Nucleic acid amplification test
OEM	Original Equipment Manufacturer
PCB	Printed circuit board
POC	Point-of-care
RIVM	Dutch National Institute for Public Health and the Environment
RNA	Ribonucleic acid
SoTA	State of the Art
UX	User experience

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Summary

Summary

Benchmark Electronics is an electronics manufacturer mainly active in the medical sector. Benchmark's office in Almelo offers customers R&D, high-tech manufacturing, and design engineering services. Through previous graduation assignments and internal projects, Benchmark has been working on a universal platform for microfluidic-based medical diagnosis. The platform is to be suitable for both research purposes and for use as a POC testing device. As Benchmark's platform is currently under development, the concept is not very clear yet, and significant parts are yet to be concretised. This thesis aims to concretise the **functions** of the platform, the **system** and its components, a preliminary **requirements** specification, **user interactions**, and most importantly establish a **design language**. For this thesis I spent twelve weeks working for Benchmark Electronics in Almelo. The results are to be used for marketing purposes, and for the continued development of the platform.

Microfluidics is the technology of manipulating very small amounts of liquid (internal volumes less than 100 µL) on a microfluidic chip. This technology allows for complete chemical processes to be embedded onto one microfluidic chip, in the form of a so-called LOC. LOC analytics has various benefits compared to traditional analytical chemistry, such as faster chemical analysis, parallel experiments, lower risk of contamination, lower reagent consumption, and lower operator skill requirements. This makes LOC technology very suitable to be used in POC diagnosis devices.

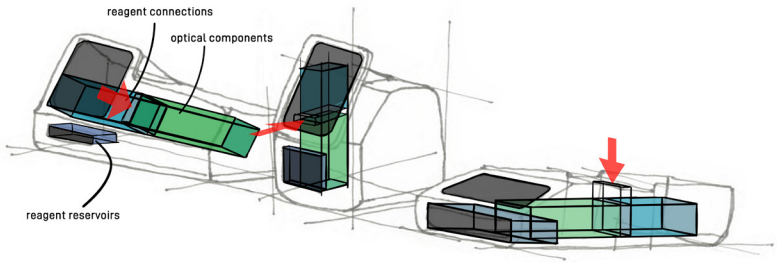
In order to perform analysis on a microfluidic chip, various chip-to-world connections need to be established to control on chip behaviour (pump liquids, provide pressure or electricity). In contrast with the competition, Benchmark's platform is capable of automatically making these chip-to-world connections, given that the chip is proprietarily developed in line with the standard. This means that the reagents necessary for the on-chip reaction with the to-be-analysed sample are administered to the chip by the device.

From this stem the basic functional requirements of the platform:

- It shall be able to accept a test cartridge and connect to the microfluidic chip.
- It shall be able to store reagents and administer these reagents to the chip when conducting a test.
- For testing, it should be able to conduct analysis via fluorescence spectroscopy.

Important next are what use-situations exist for the platform. For this, POC and laboratory-use were recognised as the most important. 1) In a POC setting, the device will be used by a medical professional like a GP or physician to carry out a medical assay for a patient. Instead of sending the sample to a medical laboratory with a long throughput time, the medical professional can carry out the test in-practice, which leads to better healthcare. For the POC use-case, tests are proprietary and predefined. 2) In the laboratory use-case, the platform will be used for the development of new microfluidic chips, complex diagnostics, and drug development. For this use-case, important is the ability to monitor reactions closely and accurately, and to be able to carry out a large variety of (not per-se predefined) tests. On top of this, the laboratory variant shall have a door for the operator to access the internals of the device.

Now that the core functions of the device and its functional variants are concretised, the project enters the design-phase. First, a general investigation was done into literature describing points of attention for designing in the medical space. This, and various form studies of existing devices, formed the basis of inspiration for exploratory ideation. Concepts where defined ranging three design directions, which were based on the *spatial orientation* of the internal mechanism components (see figure).



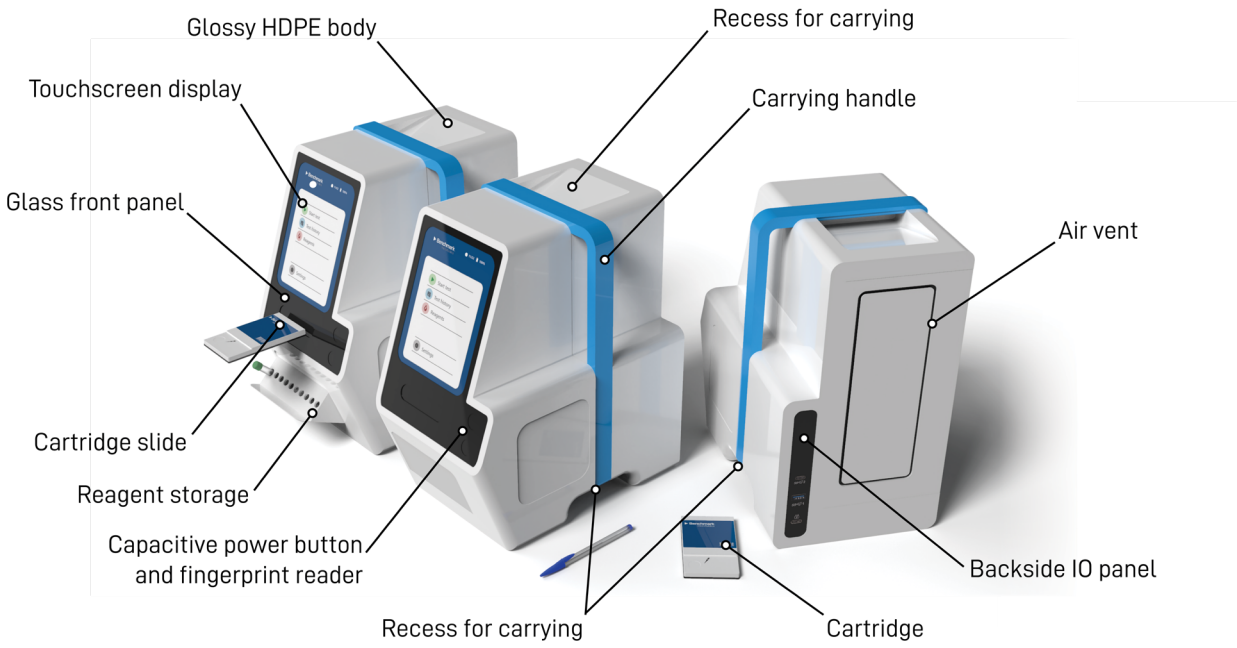
Three design directions based on orientation of components

Through various feedback meetings and continuous iterator, a near-final concept was chosen and made into a physical model (see figure on the next page). The model effectively demonstrated the scale of the device, and relevant the affordances such as the screen and cartridge slot. To test some of these affordances and key man-machine-interfaces a semi-functional mock-up was made of the UI and a small user-test was conducted, revealing some small improvements for finalizing the design.

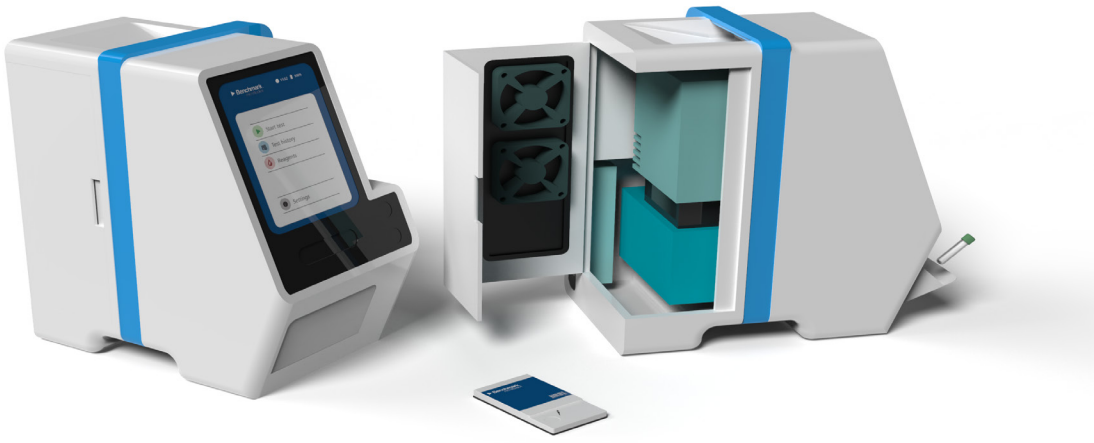
Photos of the model and the important user interactions

The design was finalized after a thorough design review. The final device (see next page) features a glossy white HDPE body with a black glass panel facing the user. Embedded within the glass are the display, capacitive finger-print-scanner and ON-button, and the reagent slide. Slightly lower, embedded in the body of the device, is the cover behind which the reagents are stored. Through here, the operator can exchange and refill reagent reservoirs. The side of the device features an interface for modular expansions, such as a module for extra reagent storage. The laboratory variant also includes a door for the operator to access the internals.

The device is relatively small, with a footprint of only 23x35 cm and a total hight of 40 cm. It is estimated to weigh under 8 kg and should be very portable with the integrated carrying handle. To aid in portability, the device includes a sophisticated power supply, with surge protector and battery. Furthermore, the chapter on future design directions describes some ideas for peripherals to the device to make it more rugged (e.g. screen protector and foam padding).



Final design and characteristics (POC variant)



Laboratory variant of the device showing operator door

Chapter 1

General introduction

1.1. Benchmark electronics

Benchmark Electronics in Almelo is part of the multinational Benchmark Electronics Inc. electronics manufacturer, mainly active in the medical sector. Benchmark offers research and development of electronics and services to original equipment manufacturers (OEMs). It also provides its customers with comprehensive and integrated design and production services and facilities, capable from initial production design through volume production and even direct delivery of the final product. Currently, Benchmark Electronics Inc. has 23 branches, across the Americas, Europe and in Asia (see figure 5).

Figure 5. Benchmark locations (green = manufacturing, orange = design engineering, yellow = procurement, blue = precision technology)

Benchmark Almelo offers services ranging from industrial design, research and development, electrical engineering, mechanical engineering, prototyping, and manufacturing. This work is limited to engineering and manufacturing services (EMS), which are offered to OEMs. The branch in Almelo has approximately 500 employees.

Benchmark is currently working on a universal platform for microfluidics diagnosis and analysis. The goal of this platform is to be as versatile as possible, for example by being compatible with variable chip sizes and by offering different ways of testing. The platform will be suitable for both research purposes and for use in the medical sector. What is interesting is that this microfluidic platform will be designed, manufactured, and shipped from Benchmark, effectively making it an OEM. This was the premise for this bachelor graduation assignment.

1.2. Problem statement

Microfluidic technology concerns itself with the manipulation of very small volumes of fluids to control chemical, biological, and physical processes [1]. By integrating all processes necessary for medical or chemical analyses, complete process-trees can be integrated into one chip: so-called lab-on-chip (LOC) devices [2] [3]. LOCs allow for a variety of conventional laboratory operations and assays to be carried out quicker than conventional, in parallel, with lower risk of contamination, lower reagent consumption, and lower operator skill requirements [4]. Thus, LOCs are very promising for point-of-care (POC) medical analysis, and for specialized laboratory tests [5].

One aspect of LOCs is that they require very specific fluid, electrical and gaseous inputs to get from the macro environment of the test-setup to the microenvironment on the chip. Since there is currently no standard within the microfluidic chip industry, this requires researchers and (medical) equipment manufacturers to design new devices with new chip connections for each specific new chip. As a result of this, the POC testing-device market has a lot of machines, each capable of very specific tests based on their own chip. For researchers, this means that a lot of time is required to configure their test-setup and specific components (e.g. heating elements, pressure chambers, or parts for analyses based on optics, fluorescence, and so on).

To solve these issues, an ISO standard for chip connections was proposed by EnablingMNT. Benchmark is in the process of developing a compatible universal microfluidic platform based on this standard. This platform should include all the necessary fluid, electrical, and gas connections to the chip, house reagents, and be able to perform a variety of analytical steps. What sets this platform apart from other chip-analysing machines is that it is not limited to one chip manufacturer. This allows researchers to design chips according to the Benchmark standard and subsequently use the platform for analysis, foregoing the need to build their own test-setups and thus significantly speeding up research. Furthermore, the platform could be implemented in medical POC situations for various diagnostic assays, based on recyclable proprietary chip cartridges.

Because of its complete and universal nature, the platform has applications in a wide variety of situations. Naturally, less-demanding use cases require less complex hardware; a research laboratory demands more functionality than a GP for quick diagnosis of their patient. Thus, it is wise to define possible

use-cases of the platform, and the components necessary for each case. Furthermore, the idea right now is still only very holistic. To continue work on the platform, it needs to be better defined in terms of use-cases, components, and design language.

1.3. Design brief

The goal of this thesis is to concretise Benchmark's initial idea for a microfluidics-based platform for medical diagnosis. Potential use-cases of the platform, and the components necessary for these are to be investigated. Based on this, a system architecture and a requirement specification are to be defined. Lastly, combining all these factors, the platform is to be designed with functional variants to cover the major use-cases.

As part of the design process, common denominators (e.g. the chip insertion mechanism) are to be investigated based on usability and human factors. Lastly, the conceptual design will be finalized with the design of a product design language for the platform. Following this, each functional variant will be designed to ensure brand values, user interaction, and design & styling are applied correctly. This will serve as a guideline for the remaining development of the platform.

Deliverables

> Identification of all the different technical components of the platform and their influence on the design.
This should form a basis for the concept design, as all components must be catered to.
> Identification of relevant use-cases for the platform (lab, medial, etc.) and their functional wishes.
This forms a basis for defining the variants within product family and for creating the requirements specification.
> Identification of which components interact directly with the user.
This forms the basis for the user experience analysis.
> User experience analysis.
As part of the design process, this forms a basis for the concept design, as human factors must be kept into account.
> Conceptual design of the platform.
This should establish a basis for the design of the platform for Benchmark to continue work on later. Broad outlines of function and form of the platform should be defined, including the design of interactions, experiences, and

processes. This deliverable should include concept sketches, a physical model (if possible) and in any case digital models and visualisations.

> Renders and marketing folder showcasing the product family and design. *Benchmark can use this for internal and external marketing, as part of the presentation materials for the final product.*

1.4. Thesis structure

This project can be divided up into four phases: 1) preliminary research, 2) system definition and concretisation, 3) conceptual design and UX, 4) finalization and presentation. The thesis follows a similar structure. An overview of project phases is presented in table 1.

First, to gain insight into the technology and applications of microfluidics, **Chapter 2** presents research findings in the form of a state-of-the-art (SoTA). Next, **Chapter 3** concretise the platform in terms of its system architecture, components, and use-cases. Following this, a comprehensive requirements specification is presented in **Chapter 4**, to serve as a guideline for design.

Chapter 5 presents the complete design process up to the final concept that was taken into final design review. It goes over the industry standard for medical design, important user-interactions, and touches briefly on the design of the graphical user interface (GUI). **Chapter 6** follows through with the design of the GUI, as it is necessary to have a working mock-up in order to carry out a usability testing scenario. **Chapter 7** presents the last changes based on the final design review and the final design. On top of this, Benchmark's sell sheet is updated with the results of this thesis. Finally, **Chapter 8** recommends further action on points where this thesis falls short because of time or scope constraints. Lastly, it also explores some fun future design directions for the platform.

Table 1: Project phases and results

1:	**2:** *system definition & concretisation*	**3:** *conceptual design & UX*	**4:** *finalization & presentation*
SoTA	▪ Use-case identification and required functions ▪ System architecture overview	▪ User interactions overview ▪ Concept design ▪ UX analyses of relevant interactions	▪ Design finalization ▪ Renders and marketing material

Chapter 2

Microfluidics State-of-the-Art

2.1. Introduction

In this section, the status quo of microfluidics, LOCs, POC testing, and research is introduced by consulting existing literature. First are introduced the concept of microfluidics, LOCs, and their applications. Next, POC testing and what are common diagnostic targets. A preliminary market research is conduced into what LOC-based POC tests are available today, especially focussed on products relevant for this research. In the same way, the chapter elaborates on the various fields or research where microfluidic chips play a large role and what techniques are prevalent for sensing and observation. Finally, the key points are summed up this section's conclusion, to be referred to when writing the requirement specification.

The literature for this review was conducted by searching Scopus with the following search query: *TITLE-ABS-KEY ((microfluidic* AND (point-of-care OR poc OR poct) AND assay* AND (loc OR lab-on-a-chip OR lab-on-chip)))* yielding 298 document results. 27 papers were selected based on age and publication type (preferably reviews). Consulting the cited works within these sources yielded more relevant papers and a comprehensive report on LOCs by the Dutch National Institute for Public Health and the Environment (RIVM). Further reading was done based on other cited works. Other sources, including but not limited to various microfluidic technology manufacturers and news articles were also used.

2.2. Introduction to microfluidics

Microfluidics refers to fluid manipulation technologies in which at least one dimension of the typical elements is less than 1 mm and internal volumes are less than 100 µL. Along with some commercial applications such as ink-jet printers, microfluidics is widely used in the medical fields of chemistry and biology. Microfluidics allows for tiny amounts of fluids to be manipulated and thus offers several advantages over conventional systems. Benefits include faster reaction time, enhanced analytical sensitivity, enhanced temperature control, portability, easier automation, and parallelization. Ultimately complete lab routines can be combined into one device or LOC [3].

Miniaturization enables researchers to create LOC devices, which are microsystems capable of integrating entire biological or chemical process-trees commonly carried out in a laboratory. LOCs benefit from the same advantages as microfluidics and additionally allow for whole biological and chemical analyses

to be integrated into one chip. This allows for faster chemical analysis, parallel experiments, lower risk of contamination, lower reagent consumption, and lower operator skill requirements [4].

These benefits allow for POC testing, where LOCs are deployed for fast lab tests to aid in medical diagnosis. Microfluidic technologies can automate various steps of medical assays, including sample preparation, reaction, transportation, and analysis, inside a single chip within minutes [6]. LOCs have been applied in many biological assays, such as electrophoresis [7], immunoassays [8] [9] [10], pathogenomics [11], nucleic acid analysis [12] [13], and cell manipulations [14] [15]. This makes POC medical assays with LOCs a very attractive alternative to traditional lengthy and labour-intensive laboratory tests.

2.2.1. Microfluidic chips

A microfluidic chip is generally a device which allows for the manipulation and scrutinization of fluids, as described above. Chips are usually transparent and made of thermoplastics such as acrylic, glass, polymers, or silicon (PDMS). Figure 6 presents an example chip. Chip thicknesses range from 0.5 mm to 5.0 mm, and dimensions vary. Chips have internal microchannels, wells for fluid mixing, pumps, valves, and so on [16]. To facilitate these operations, micro-to-macro connections are present to provide reagents, gasses, and power to the chip. These inlet/outlet connections are referred to as the chip-to-world interface. The chip-to-world interface can be subdivided into three categories: fluid, pneumatic, and electrical connections. Typically, fluid and pneumatic connections can be seen as one, as their requirements (airtight, minimal dead space, etc.) are similar [17]. There are few companies currently supplying specialized components like connectors, tubing, valves, pressure regulators, and so on.

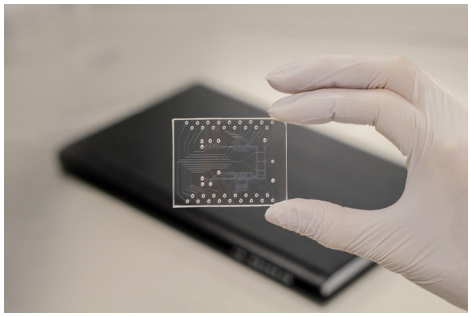


Figure 6. Microfluidic chip (image taken from uFluidics [16])

Design guideline

To facilitate the process of designing new microfluidic solutions, the leading institution for micro- and nano-technology EnablingMNT presented a white-paper suggesting a design guideline for microfluidic devices and chip-to-world interfaces [18]. They distinguish between single- and double microscopic slide formats, and credit-card format. Most importantly, they propose a standardized chip-to-world connector grid of 3.0 x 3.0 mm.

Based on this (proposed) standard, Wouter Vreemann has developed a standardised cartridge for Benchmark in a previous graduation assignment to be used with the platform [17]. His cartridge system will be used for the platform under design.

2.2.2. Sensing techniques

The most common techniques to monitor on-chip behaviour are optical detection, electrochemical analysis, interferometry, and spectroscopy. Prevalent detection targets are chromatography, absorbance, fluorescence, and chemiluminescence.

Optical detection

Perhaps the simplest method is simply visually inspecting the sample and its chemical reactions over time. This is commonly done using a microscope (sometimes with camera), or simply with a camera of sufficiently high resolution, foregoing the need of extra lenses.

With bright-field microscopy (where the sample is illuminated by external light), the shape, size, colour, trajectory and other status of droplets within the microchannels can be visualized conveniently [19]. Attaching a high-speed camera allows for time-based analysis and time-lapses showing the physical status of droplets with sub-millisecond resolution.

Chromatography (linear or 2D) is a very commonly executed test which lends itself perfectly to optical detection. The principle of chromatography is simple: a sample mixture is separated by passing it through a medium in which the components move at different rates [20]. Chromatography is suitable for the detection of various proteins (d-dimer, HbA1c, troponin etc.), sugars, and other components of a mixture. It is also the basic technique for lateral flow (immunochromatographic) tests.

Spectroscopy

Absorbance is the attenuation of radiation as a function of its wavelength and is measured with a spectrophotometer. Here, the sample is exposed to light of broad range of wavelengths, and the absorbance percentage is measured for each wavelength.

Next, fluorescence can be measured via emission spectroscopy. For this, the sample is exposed to light of specific wavelengths causing photoexcitation of specific luminescent molecules (luminophores). The light emitted from the luminophores can similarly be measured with a spectrophotometer to calculate the absorption and emission spectrum of the sample, and thus the concentration of luminophore analytes therein [21].

Chemiluminescence is the emission of light as a result of a chemical reaction. The emitted light can be measured simply with a luminometer. A luminometer generally works with very small samples and can detect even a handful of photons. In contrast to absorbance or fluorescence, chemiluminescence does not require an excitation light source [22].

Lastly, Raman spectroscopy is based on the principle that specific chemical bonds scatter light. For this, a high intensity single-wavelength laser is directed onto the sample. Most of the scattered light is of the same wavelength as the laser (Rayleigh scattering), however a small fraction will be influenced by the molecular bonds of the sample. Rayleigh scattered light is filtered out while the rest is detected by a spectroradiometer, revealing the chemical structure of the sample [23].

Mass spectrometry

Mass spectrometry (MS) can detect the samples qualitatively and quantitatively by measuring the mass-to-charge ratio of ions. To test, the sample is (partly) ionized and the ionized particles are removed by an extraction system and guided through a detector. The results are a plot of intensity as a function of the mass-to-charge ratio and can be used to determine the masses of molecules, and to identify the chemical identity of molecules and compounds [24]. According to Y. Zhu, “compared with other detection techniques, MS provides outstanding advantages including label-free detection, capability of elucidating chemical structures with fragmentation, high sensitivity, and simultaneous detection of multiple analytes” [19]. This makes it a very attractive method of chemical analysis.

2.3. Point-of-care testing applications

Microfluidic technology has broad applications in healthcare and rapid diagnostics. Specifically developed chips and accompanied devices offer quick diagnostics in POC settings, such as the doctors' office, intensive care unit (ICU), and operating room. Current widespread tests include urine pregnancy, hemoglobin, and CRP tests, and are conducted usually through cheap disposable lateral flow strips [5] which employ basic microfluidics in the form of a microchannels on a porous surface (capillary bed). Some specialized LOCs are already used for more advanced POC testing, mostly for immunoassays and pathogenomics. Such devices are prevalent for antigen or antibody assays, which can be done with whole blood, urine, or throat swab [25].

A promising area where microfluidics and LOC technology presents a revolution is in immunodiagnostics. Typical diagnostic procedures often require chemical or biological assays that rely on costly equipment and take long to perform [26]. LOCs bring molecular diagnostics and immunodiagnostics into the POC environment, allowing for quick diagnostics at the bedside or in the doctor's office from only very small untreated samples (as low as 1 µL) [27] [28]. Only few of such devices are in use today.

2.3.1. Diagnostic targets

LOCs can be used to replace traditional laboratory testing and diagnostic assays in medical settings at the POC. Although new chips with increasingly more applications are continually developed, this paragraph gives an indication of the types of diagnostic targets that can or may be detected through LOC technology.

Proteins

In immunodiagnostics, LOCs are currently used to detect antigen-antibody binding. Many diseases are associated with the presence of various protein species, including enzymes, antibodies, and hormones. Most commonly tested are glycated haemoglobin (HbA1c) for diabetes mellitus, CRP for inflammation or bacterial infections, D-dimer for thrombosis, troponin for injury to the heart, and viral-infection markers for HIV, influenza, chlamydia, and hepatitis [29].

Metabolites and small molecules

Metabolites are intermediate or end products of metabolism reactions (converting food to energy or proteins) and are good indicators for many common diseases. Most commonly targeted for testing are glucose for diabetes mellitus,

cholesterol and triglyceride for cardiovascular disease, lactate for blood oxygenation, and ammonia, creatinine and urea for renal dysfunction [30].

Nucleic Acids

Nucleic acid diagnostics measure Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) in order to investigate the genetic details of a patient or nucleic acid sequences of invading pathogens [29]. Polymerase chain reaction (PCR) is often part of these assays and is used to rapidly copy a specific sample and amplify it enough to enable studies. These tests are among the most complex, since they require additional steps for sample pre-treatment (e.g. cell sorting, isolation, etc.).

Cells

LOC diagnostics allows for identification and counting of (human) cells in blood and other samples. In addition to basic blood-cell counting, M. Toner describes that "cell-assay-based devices could implement diagnostic and prognostic testing for infectious diseases, cancers, inflammatory responses, and haematological parameters" [31].

2.3.2. Current point-of-care devices

An inventory of current LOC applications is presented in annex 1 (adapted from the RIVM [5] with permission). It comprises 60 companies with a total of 168 devices on the market, and 9 under development. Many of these applications involve handheld devices for blood glucose testing, HIV diagnostics, or electrolytes analysis.

Only devices that can carry multiplex assays from a single untreated sample are relevant for this project (i.e. not simple handheld glucose meters). Prominent devices currently on the market that fit this criterium are listed in table 2 and elaborated upon in more detail. The leading companies that develop relevant hardware are Abbott, Abaxis, and Bosch. Startup Abionic's abioSCOPE is also listed below, as it was manufactured by Benchmark and poses functionality similar to the system under design.

Table 2. Current POC devices and operating principles

Manufacturer	Device	Available tests	Analyzer hardware	Principle	Detection method	L/N†
Abbott Point of Care Inc.	Piccolo Xpress	ALB, ALP, ALT, AMY, AST, BUN, Ca, CHOL, CK, eGFR, Cl-, CRE, CRP, DBIL, GGT, GLU, HDL, K+, LAC, LDH, LDL, nHDLc, TBIL, tCO_2, TP, TRIG, UA, VLDL, Na+ [1]	- Heater - Centrifuge - Xenon arc stroboscopic laser - Beam-splitter - Spectrophotometer	Reagents are designed so the analyte reaction produces specific chromophores that absorbs light of known wavelengths [2].	Absorption spectroscopy	N
	ID NOW	COVID-19, Influenza A/B, RSV, STREP [3]	- Heater - Centrifuge - Ultraviolet lamp - Spectrophotometer	Reagents multiply strands of nucleic acid specific to a known bacteria or virus. Specific molecular beacons latch onto the replicated strands of nucleic acid and produce fluorescent light [4].	Emission spectroscopy (fluorescence)	L
	Afinion 2	Haemoglobin A1c, CRP, ACR, CHOL, HDL, LDL, Trigclicerides [5]	- *Heater* - *Laser* - *Spectrophotometer*	*Reagents are designed so the analyte reaction produces specific fluorophores that emit light of known wavelengths.*	*Emission spectroscopy (fluorescence)*	N
Bosch Healthcare Solutions GmbH	Vivalytic	Influenza A/B, Adenovirus A/B/C/D/E, Bocavirus 1/2/3, Coronavirus 229E/NL63/OC43/HKUI, Enterovirus A/B/C, Metapneumovirus, Parainfluenza 1/2/3/4, RSV A/B, Rhinovirus A/B/C, CT, NG, TV, MG, TP, HSV-1, HSV-2, HD, MH, UU, various bacteria and fungi, and antibiotic resistance markers [6]	- Heater - High resolution camera - *Laser* - *Spectrophotometer*	DNA amplification via qPCR and identification of specific nucleic acid strands via µArray and detection based on fluorescence [7].	Molecular diagnostics, emission spectroscopy (fluorescence)	N
Abionic SA	abioSCOPE	D-dimer, cTnI, ProBNP, CK-MB, hsCRP, PSP, CRP, PCT, C. difficile ToxA/B, Dengue virus NS1 and IgM, HIV, Zika, Ebola, SARS, Influenza A/B, CT, NG, GBS, TV, ALP, AST, ALT, ALB, pH, pCO_2, pO_2, sO_2, K+, Na+, Ca_2+, Cl-, LAC, UA, CRE, IgE, tryptase, TSH, HCG, GLU, HbA1c, ferritin, haemoglobin, erythrocyte, white blood cells, neutrophils, basophils, eosinophils, lymphocytes, thrombocytes, various respiratory tract infections, antibiotic resistance markers, and antibodies [8]	- *Heater* - *High resolution camera* - *Spectrophotometer*	**DNA**: amplification *via qPCR* and identification of specific nucleic acid strands *via µArray* and detection based on fluorescence. **Cells**: sample separation with flow cytometry and detection based on fluorescence. **Antibody/antigen**: immunoassay with specific reagent *and detection based on fluorescence* [8].	Molecular diagnostics, electrochemistry, emission spectroscopy (fluorescence)	N

†L/N = *qualitative/quantitative results.*
Italics: assumptions based on industry standard as no technical information was available.

Abbott Abaxis Piccolo XPRESS

The Abaxis Piccolo XPRESS (figure 7) is capable of conducting various blood chemistry tests using a spectroradiometer. Its functionality is based on single-use plastic discs, which contain the required liquid diluent and freeze-dried reagents. Abbott currently sells a total of 16 discs, each performing a variety of tests. To perform, the operator applies a sample of whole blood onto the appropriate disc and inserts it into the machine. The disc is then centrifuged, which dilutes and distributes the sample through microfluidic capillary channels using centrifugal force. The absorbance is measured by a laser that measures the reactions via absorption spectroscopy using nine wavelengths simultaneously. The results are ready within 13 minutes, printed from the top of the device or exported to a computer via USB [32].

Testing discs house a variety of tests, grouped into sets directed at specific diagnoses. Abbott's assortment includes discs to assess metabolic activity, liver and kidney function, lipid profile for cardiac disease, renal function, and so on. All discs combine tests for multiple diagnostics targets, as if running multiple laminar flow strips simultaneously. Most testing discs adhere to the American Clinical Laboratory Improved Amendments (CLIA). Shelf life ranges from 9 to 18 months depending on the disc.

The Piccolo XPRESS analyser has a retail price of 20 500,00 USD. Panels cost between 80,00 USD and 168,00 USD [33] [34].

Figure 7. Piccolo Xpress analyzer and disc (image taken from Abaxis [35])

Abbott ID NOW

The Abbott ID NOW (figure 8) utilizes nucleic acid amplification test (NAAT) technology for qualitative identification of genetic markers for infectious diseases. The device requires the use of single use so-called Test Bases and Sample Receivers to run each assay. To perform, the operator inserts the Sample Receiver and Test Base into the machine. The sample is then taken from nasal-, throat-, or nasopharyngeal swab and added to the Sample Receiver. Genetic code is amplified via PCR as rotation, heating, and detection are provided by the machine. Results are qualitative, and based on fluorescently labelled molecular beacons, which detect each of the amplified RNA targets [36] [37]. Results can be viewed on screen or extracted via USB withing 2 to 52 minutes, depending on the test. The testing cartridges adhere to CLIA.

ID NOW is capable of testing for various viral infections such as Influenza A & B2, Strep A, Respiratory syncytial virus (RSV), and since recently SARS-CoV-2 (novel coronavirus).

Data on the retail or per-test costs is unavailable.

Figure 8. Abbott ID NOW (image taken from Abbott [38]

Abbott Afinion 2

Afinion 2 (figure 9) is mainly directed to the detection of physiological diseases like diabetes mellitus, obesity, and kidney failure. The device promises results between 3 and 5 minutes, is factory calibrated, and is capable of self-checking with integrated error detection. Testing requires single use test cartridges.

To perform, the operator uses the collects a patient's sample of whole blood and inserts it into the correct cartridge. The cartridge is then inserted into the machine. PCR happens automatically and detection is done via fluorescent emission spectroscopy. The results are displayed on screen or exported wirelessly. After testing, the cartridge is discarded.

Abbott currently stocks four test cartridges, capable of testing for Haemoglobin A1c (diabetes), a broad range of lipids (artery disease, heart attack, stroke), CRP (inflammation), and ACR (kidney failure), respectively. Cartridge shelf time is 3 months at room temperature. All tests are adherent to CLIA.

The Afinion 2 analyser has a retail price of 5 000,00 USD. Test cartridges cost between 61,00 USD and 153,00 USD [39].

Figure 9. Abbott Afinion 2 (image taken from Abbott [40])

Bosch Vivalytic

The Vivalytic (figure 10) is an open platform for molecular diagnostics. This means independent test providers can design tests in the form microfluidic chips around the interfaces present in Vivalytic. Tests are integrated into cartridges and sold on a per-test basis. Arguably, these characteristics make it Benchmark's biggest competitor. Currently partnering with Bosch are R-Biopharm and Randox Biosciences [41]. To perform, the operator collects a sample of whole blood, urine, sputum, nasal or throat swab onto the cartridge. The cartridge barcode is then scanned before the cartridge is inserted into the device. Genetic material is amplified via PCR automatically, testing done by fluorescent emission spectroscopy, and the results are displayed on screen or can be exported via USB.

Currently on offer are assays manufactured by Randox. Tests are standardised cartridges, with integrated microfluidic biochips. Randox has developed tests for bacterial, viral, hospital acquired, and sexually transmitted infections. For a full list of tests see www.randox.com/vivalytic [42]. Cartridge shelf life is two years at room temperature.

Data on the retail or per-test costs is unavailable. Distribution of the device started in July 2019.

Figure 10. Bosch Vivalytic (image taken from Bosch [43])

Abionic abioSCOPE

The Swiss start-up Abionic developed abioSCOPE (figure 11) based on nano-fluidic chips. That means flow channels are even smaller than in microfluidic chips: even “at the nano-scale many dimensions of molecules are of similar size as the nano-fluidic channels that constrain them” [44]. AbioSCOPE forces molecules into a nanochannel to allow for fast immunoassays analysing up to 14 parameters at the same time from a single drop of blood. An optical system based on fluorescent emission spectroscopy is used for biomarker detection [45].

AbioSCOPE is capable of a variety of assays for infectious and cardiovascular disease, immunology, critical care, and drug monitoring. Furthermore, it can conduct allergy tests within 5 minutes. Analyses times vary between 1 minute and 8 minutes for ‘simple’ immunoassays, while complex molecular diagnostics for infectious diseases can take up to 30 minutes [46].

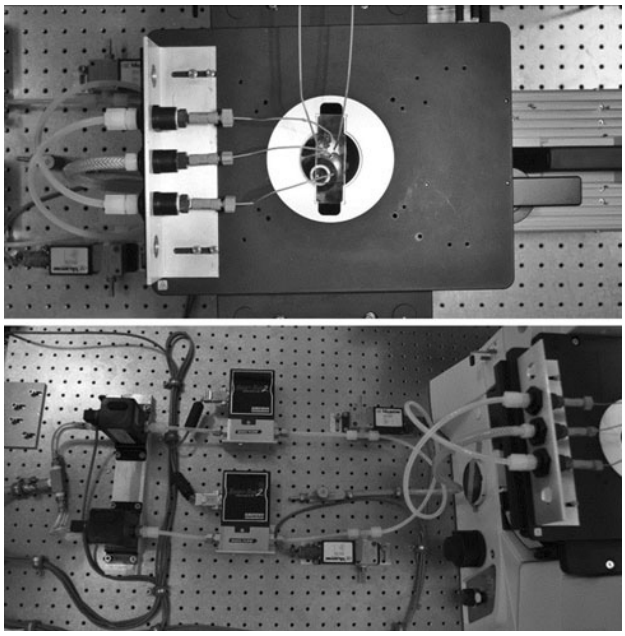
The device requires the use of single use so-called abioMIX and abioKIT to run each assay. To perform, the operator must take a sample of whole blood and mix with the abioMIX. The sample is than pipetted on the selected abioKIT. Next, the abioKIT is inserted into the machine. Analysis is done automatically, and the results can be extracted on an SD-card. Shelf life for the abioKIT and abioMIX is about 6 months [47]. AbioSCOPE is CE certified.

Data on the retail or per-test costs is unavailable.

Figure 11. Abionic abioSCOPE (image taken from Abionic [48])

2.4. Research applications

In contrast to POC microfluidic devices, for research, chip-to-world connections need to be made manually and configured for any new chip. Researchers typically spend considerable amounts of time building their test-setup (figure 12) to allow for specific tests and measurements to be conducted. This slows down critical lab procedures like such as the development of new chips, drug discovery or clinical diagnostics significantly. In contrast to the medical devices, there are no clear-cut devices specifically designed for research use. Instead, typical laboratory research applications for microfluidics are listed on the next pages.



The upper image shows a microfluidic mixing device secured to a microscope stage with integrated gas and liquid delivery lines. The lower image shows the pressure regulators, flow meters, pressure transducers, and backpressure valve used for controlling gaseous flow. Liquid flow is issued from a constant displacement syringe pump (not shown). Image and description taken from Carroll B. [41].

Figure 12. Top-view images of a microfluidic test bench

Diagnostics and assays

As described above, microfluidics and LOCs have broad applications in diagnostics. In contrast to POCTs, tests done in a laboratory can be more time-consuming and more detailed, e.g. by using more sophisticated measuring methods. Emerging fields here are cellular assays and organs-on-a-chip technology. In these cases, the tissue and analytes need to be constantly kept in an adequate surrounding, to maintain their viability and activity [49]. These tests and simulations are interesting to investigate the effectiveness of different

dosing concentrations, and its effect on toxicity, side effects, and so on. Such applications require high throughput, the ability to precisely control the test environment (pressure, temperature, etc.), and low reagent consumption [50].

Drug discovery

Next to diagnostics, the largest market segment in the pharmaceutical research industry is drug discovery. Here, new promising drug candidates (hits) are identified by high-throughput screening (HTS), and then validated [51]. For hit validation, there has been increased interest in cell-based screening and assays [49]. For this, microfluidic devices have been designed to perform continuous-flow biochemical and cell-based assays. These devices reduce reagent consumption significantly [52]. This market segment requires high throughput, and sophisticated methods of biomarker detection (ELISA, fluorescence, reflectance, spectroscopy).

Chip development

Especially exciting is the laboratory testing and development of new-for-production POC microfluidic-, bio-, and LOC chips. Before entering the POC market, chips and tests need to be extensively tested and validated to ensure minimal erroneous results. This process also includes testing for health standards, CE marking, and CLIA.

2.5. Conclusion

Microfluidics has concrete benefits when compared to traditional fluid handling. It allows for faster reaction time, enhanced analytical sensitivity, enhanced temperature control, portability, easier automation, and parallelization. This makes it a very attractive technique to employ in the medical and chemical industry. Microfluidic chips are designed to carry out specific operations, or a series of operations. Furthermore, combining biological or chemical process-trees onto one chip allows for the creation of LOCs. To facilitate these operations, micro-to-macro connections are present to provide reagents, gasses, and power to the chip. A whitepaper by EnablingMNT proposes a design standard for chips, aiming to standardize chip-to-world interfaces. The platform under design will follow this standard.

Microfluidic technology is already commonplace in the medical and research industry and sees wide applications in diagnostics and the development of new drugs and chips. The research sector struggles with the chip-to-world interface and connecting sensing techniques to the chip since there is cur-

rently no accepted standard. Especially drug discovery requires sophisticated methods of biomarker detection, such as optical detection, various forms of spectroscopy, and mass spectrometry. This adds considerable complexity to the test setup. As a result of this, researchers spend a significant amount of time on the design and construction of their test-setups.

Next to research applications, LOC technology allows for the miniaturization of complex laboratory procedures, which facilitates POC testing and assays. This is seen as a revolution for medical diagnostics and personalized medicine. The POC market is saturated with single-test devices, however there are few devices that can carry out multiplex assays with one sample. These advanced multiple-diagnosis devices all operate with samples collected onto single-use test cartridges, which contain all the reagents, microfluidic channels, and are prepared for each test. Since microfluidic chip technology is constantly evolving, it is more economic to design a platform which can accommodate all new chips, instead of building new analysis devices around new chips. However, in the POC market, usually the diagnosis device is designed around a specific new (set of) microfluidic chips/cartridges, resulting in many devices that are each capable of few tests. An exception to this is Vivalytic by Bosch, which is instead designed to be a flexible open platform for new tests to be designed around. This makes it Benchmark's largest competitor for this project.

Chapter 3

System Architecture

3.1. Introduction

A clear overview of the system's components, functions, and interfaces is paramount for proper design, especially if the project requires a multidisciplinary approach [53]. Since Benchmark's Microfluidics platform is complex in nature as it requires complex reagent management, cartridge connections, and sensing operations, it is wise to clearly define the required components and their interfaces.

This section introduces the Benchmark microfluidic system and its components. First, the system's use will be described via scenarios. Next, wishes are derived from the two use-environments and documented in a table, along with their implications on the design and functionality of the device. Based on a functional block diagram, functions will be listed in a functional overview, to serve as a basis for the system architecture overview, which details on the necessary components and interfaces. Based on this, the functional variants will be defined.

3.2. Use analysis

It is obvious the use of the device can be divided into two categories: laboratory and POC. Both categories are elaborated upon below.

3.2.1. Point of care

Use of the platform at the POC happens with one clear goal in mind: fast assays for diagnostic tests that would otherwise be outsourced to an off-site medical laboratory. Amongst primary case clinicians, there is a clear demand for POC tests. This is exemplified by a survey conducted by Howick et al. that concludes the current most frequently used POC tests only partially correspond with the desired diagnostic targets. More importantly they also state there is a need for more POC tests that can assist clinicians with immediate decisions [54].

It is clear this last point is what drives development of POC devices; immediate in-clinic testing lowers diagnostic delay, and thus speeds up decision making (e.g. urgent referrals, decision to treat with antibiotics, etc.), ultimately improving healthcare overall [55] [56]. We should therefore focus on fast, accurate results.

Users include primary care physicians, general practitioners (GPs) and their assistants, and emergency room staff.

Primary care office scenario
Goals: fast diagnosis, effective patient care

John is a Dutch primary care doctor. He shares his practice with another GP and employs several assistants. John's practice daily uses haemoglobin tests to screen for anaemia and blood glucose tests for diabetes mellitus. If John suspects on of these conditions in a patient, he instructs one of his trained assistants to conduct the test.

John's assistant fetches the patient from the waiting room and takes them aside into a vacant room. After disinfecting their hands, the assistant draws blood from the patient and labels the sample. The patient is then dismissed, as the assistant will carry out the test while they wait.

They fetch the blood-assay test cartridge from storage, check the cartridge expiry date and ensure unbroken seal. If in order, the assistant then punctures the seal and places a drop of the blood sample into the receiver on the cartridge. Next, they turn on the analytical device and they input/scan the patient ID, based on the device's instructions. When the device prompts to, they insert the cartridge into the receiver.

When the test is complete, the results are automatically exported to the office's intranet into the correct patient's dossier. If prompted by the assistant, the results are also printed by a connected/integrated printer. The patient hands the report to John. Next, as the device prompts to, the assistant extracts the cartridge and discards it. De device is now ready for the next test, and the printed report is handed to John.

John calls back the patient into the consultation room and discusses with them the results. With knowledge of the results, the GP may issue the patient with antibiotics, change their doses, stop treatment, etc. based on their discretion.

Key operator steps in this scenario

1. Disinfect hands
2. Draw blood sample
3. Label sample
4. Fetch correct test-cartridge
5. Check expiry date
6. Ensure unbroken seal
7. Place sample
8. Input patient ID to device
9. Insert cartridge into device
10. Export results
11. Extract cartridge
12. Discard cartridge

3.2.2. Laboratory

In contrast to the POC setting, laboratory use of the platform has less of a focus on speed. More important is the ability to monitor reactions closely and accurately, and to be able to carry out a large variety of (not per-se predefined) tests.

The platform could play a role in complex diagnostics outsourced from POC settings, drug discovery, and microfluidic chip and technology development. Especially the latter two set apart this use-environment, as they require a large variety of chip-to-world connections and sophisticated detection methods. What is also required more so in research than POC settings is the ability to perform multiplex testing. Next, device footprint is limited, due to the often-limited space in laboratories.

Users include medical and research laboratory staff.

Research laboratory scenario
Goals: high precision, fast throughput, good data export functionality

> *Emma works for a pharmaceutical company in research and development and is testing a new chip lay-out which could make fluorescent analysis more efficient. The new chip is designed according to the platform standard; however, it uses different reagents than the previous design.*
>
> *After decontaminating and entering the clean room, Emma fetches an empty cartridge and checks it for unbroken seal. She then unseals the cartridge and positions the chip in the right location.*
>
> *When the chip is correctly positioned, she closes and reseals the cartridge. She then turns on the analysis device and inputs the test number and parameters*

(chip-to-world interfaces, reagents, dosing, etc.). She enables fluorescent measurement along with microscopic observation.

The device prompts her to exchange a reagent storage reservoir, to accommodate for the new reagents. The device indicates which reservoir to swap. Emma takes a new reservoir and ensures for an unbroken seal. She then pipettes the new reagent into the reservoir and enters the reservoir into the device. She confirms on the touchscreen that the reservoir has been exchanged. Next, she inserts the cartridge into the device as prompted and presses the button to start the test.

While running the test she views the results on screen. When complete, she also chooses to export a detailed data report and the captured microscopic video to a connected computer. When the device prompts to extract the cartridge, she takes it out and discards it for cleaning. She is then ready to prepare the next test.

Key operator steps in this scenario

1. Fetch cartridge
2. Ensure unbroken seal
3. Place chip
4. Input test parameters to device
    a. Chip-to-world interfaces
    b. Reagents
    c. Dosing
    d. Sensing method
    e. Temperature
    f. Pressure
5. Extract reagent reservoir
6. Fetch unused reagent reservoir
7. Ensure unbroken seal
8. Fill unused reagent reservoir
9. Insert new reagent reservoir
10. Insert cartridge into device
11. Export results
12. Extract cartridge
13. Discard cartridge

Wish implication matrix

Here, stakeholders' wishes and respective implications on the design of the platform are indexed. This may serve as a basis for the requirement specification and design guidelines. The results are shown in table 3.

In the table, wishes are divided among the POC setting, laboratory setting, and both. The next two columns (functional implications and design implications) distil from this the implications on the functions and design of the platform, respectively. Actions needed, like 'add as requirement' or 'investigate options', follow from these implications and conclude the matrix.

Table 3. Wish implication matrix

	Wishes	Functional implications	Design implications	Actions needed
Point-of-care	Specific tests		Test selection should be appropriate‡	**Investigate** what tests are common and how they can be distributed over multi-test cartridges
	Fast results	Test-time should be minimised, but at maximum fifteen minutes[a]		Add to requirements specification
	Minimal maintenance	Integrated error-sensing mechanism and cleaning procedure	Device and cartridges should be robust and minimise moving parts	Add to requirements specification and design guidelines
	Simplicity	Device should give clear instructions of use and inform clearly in case of error	Intuitive interface	Add to requirements specification and design guidelines
	Simplicity	No need to insert custom reagents†		Add to requirements specification
Laboratory	Large set of sensing methods	Should be able to perform common laboratory observations‡		**Investigate** what sensing methods are most used
	Excellent accuracy and precision	Accurate sensing equipment		Add to requirements specification
	Sterile environment		Easily cleaned design	Add to design guidelines
	Multiplex testing	Multiplex capabilities[b]		
	Custom reagents	Operator should be able to add own reagents†		Add to requirements specification
Both	High test repeatability	Accurate sensing equipment		Add to requirements specification
	Minimal size		Device dimensions should be appropriate for each use-environment	Add to design guidelines
	Fast throughput	Time between test should be minimised, but at maximum one minute[c]		Add to requirements specification

[a] *fifteen minutes is seen as an appropriate maximum waiting time for the patient*
[b] *more so a requirement of the test chips than of the device*
[c] *after ejection of a test-cartridge, internal reset mechanisms should take at most one minute to prepare for the next cartridge insertion/test*
† *conflict*
‡ *likely conflict (having more methods of observation does not necessarily mean more appropriate tests can be performed)*

3.3. System architecture

3.3.1. Functional overview

To define a clear system architecture with all necessary components, the system's functions need to be defined first. For this, figure 13 presents a functional block diagram of a generic cartridge test. This allows us to index the all the functions that should be divided among components. Since the general testing procedure is the same for the POC and laboratory variants, this diagram holds for both.

It is clear the system has four major points of contact with the operator: 1) patient/sample data collection, 2) insertion/ejection of the cartridge, 3) reagent storage, and 4) display of results. These, along with the necessary functions to run an analysis, comprise the core functions of the system. Next, power supply and surge protection are grouped as utility functions, as they do not directly contribute to, but merely facilitate the other processes. The functions are listed and elaborated upon further in table 4.

3.3.2. Component overview

Next, the functions are divided into categories (sensing, pneumatics, electronics, man-machine interfaces) and allocated to subsystems and components in table 5. Each component has a space requirement. Subsystems that have additional design implications are listed in table 6.

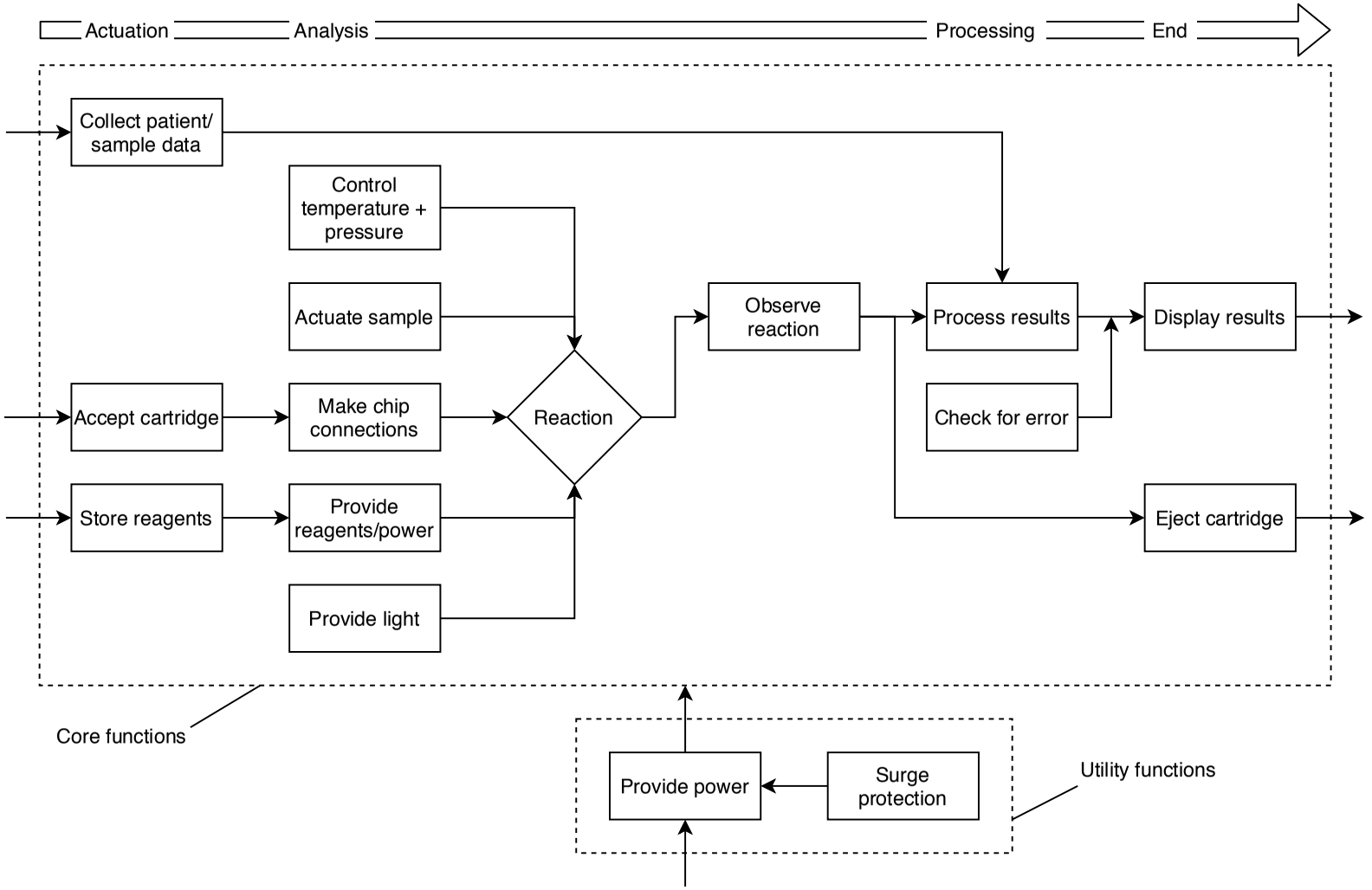


Figure 13. Functional block diagram of the microfluidic platform under design (based on process steps for generic test from left-to-right)

Table 4. System functions and descriptions

Stage	Function	Description
Actuation	Accept cartridge	Insertion of the cartridge into the machine, identification of cartridge/test type.
	Collect patient/ sample data	Input of patient or sample identification number into the machine for labelling of the test and for archiving purposes.
	Store reagents	Fluid reagent storage and refilling.
Analysis	Control temperature + pressure	Precise temperature control of the sample and chip and/or reagents.
	Actuate sample	Actuation of the sample and reaction e.g. by ultrasonic sound, heat shock, etc.
	Make chip connections	Identification and activation of required fluid/ pneumatic/electrical chip-to-world connections based on cartridge type
	Provide reagents/ power	Pressure and valve control to provide reagents to chip. Electrical control to provide power to chip.
	Provide light	Setting of light intensity and wavelength based on cartridge type.
Processing	Observe reaction	Spectroscopic measurements of reaction. Actuation of camera/microscopic optical stage.
	Process results	Results processing into usable data format.
	Check for error	Error checking based on calibration and expected results.
End	Display results	Results display on screen. Output to peripherals like computer, printer, SD-card, etc.
	Eject cartridge	Ejection of the cartridge

Table 5. System function-component pairing

Cat.	Subsystem	Components	Function(s)
Sensing	Optics	(XYZ) lights/laser stage Spectrophotometer Spectroradiometer Luminometer High-resolution camera	Provide light Observe reaction
	Speaker		Actuate sample
	Heating element		Control reaction temperature
Pneumatics	Air manifold	Pressure source Pressure controller Valves	Provide reagents
	Liquid manifold	Pump Flow-rate controller Valves	Provide reagents
	Pressure controller		Control reaction pressure
Electronics	Power supply unit	Power supply Surge protector Power distribution	Provide power Protect from power surge
	Printed circuit board (PCB) assembly	Hardware controller Data processor	Process results Check for error
Man-machine interfaces	Cartridge mechanics	Cartridge connections Cartridge identifier	Accept cartridge Eject cartridge Make chip connections Identify cartridge type
	Reagent storage unit	Reagent storage reservoirs Refilling interface	Store reagents
	User interface	Touch screen Physical buttons Peripherals (computer via e.g. USB) (Scanner) (Printer)	Collect patient/sample data Collect test parameters Display results Collect patient/sample data

Table 6. Component design implications

Subsystem	Design implications
Speaker	Sound insulation
Heating element	Heat insulation
Air manifold	Pressure chamber
Pressure controller	Pressure chamber
Power supply unit	Active cooling, heat exhaust
PCB assembly	(Active cooling)
Cartridge mechanics	Human-machine interface, appropriate affordances
Reagent storage unit	Human-machine interface, appropriate affordances
User interface	Peripheral ports

3.3.3. Preliminary system overview

Benchmark has already designed a preliminary system architecture overview (figure 14). This diagram shows some of the necessary components such as what they call the connection cartridge, manifolds for air and reagent liquid, a PCB assembly, liquid reservoir, pressure- and power source. It also documents some of the required interfaces between components, categorised into power, data, and physical connections. While this diagram is a good start concretising some of the required components, some functions are not represented. For instance, this architecture omits completely the required systems for monitoring the reaction.

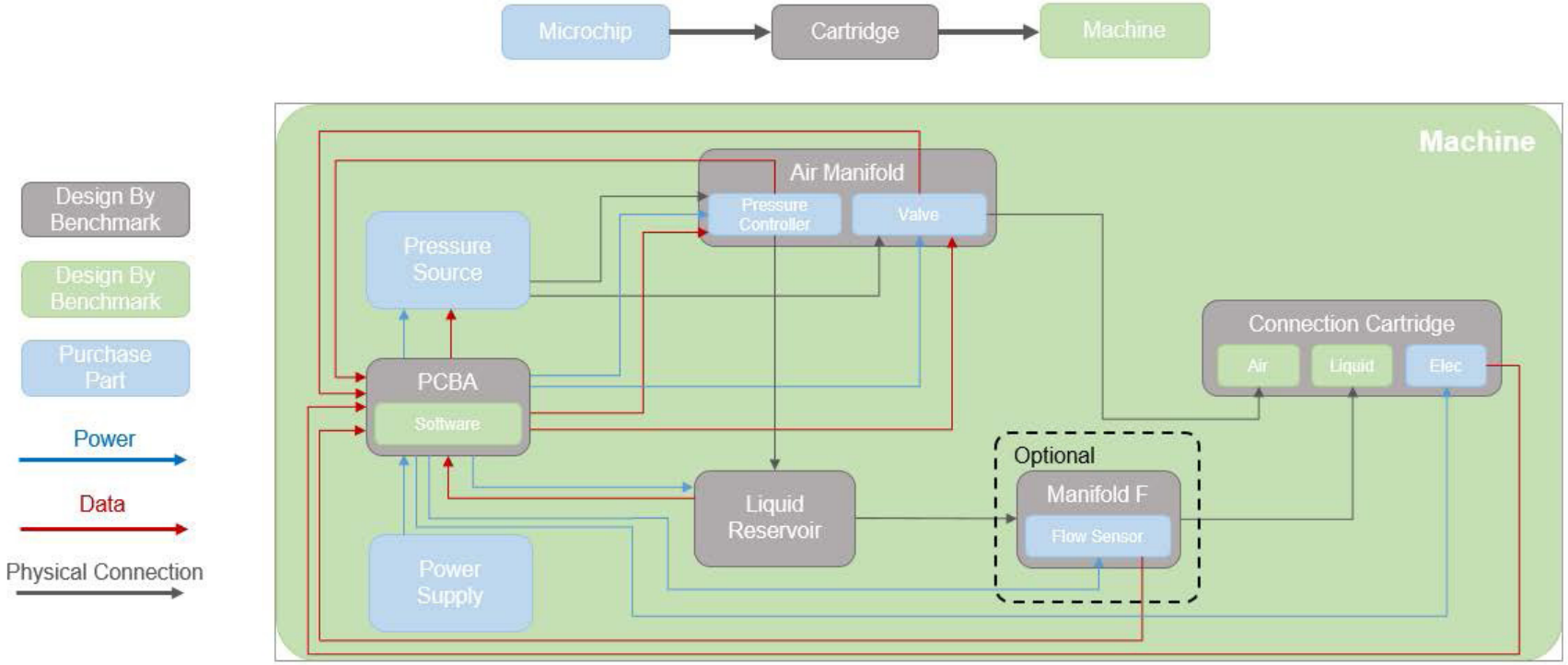


Figure 14. Benchmark's preliminary system architecture diagram

3.3.4. Improved system architecture diagram

Based on the function overview and function-component pairing, we can improve on this preliminary system overview. Figure 15 presents the improved system architecture. As with the preliminary diagram, connection types are categorised and colour coded (see legend). Subsystems are coloured based on category and components depicted as white bubbles within the subsystems. It is important to note that apart from the man-machine interfaces, this thesis will not touch much on many of the subsystems, as the specific functionalities are beyond the scope of this project.

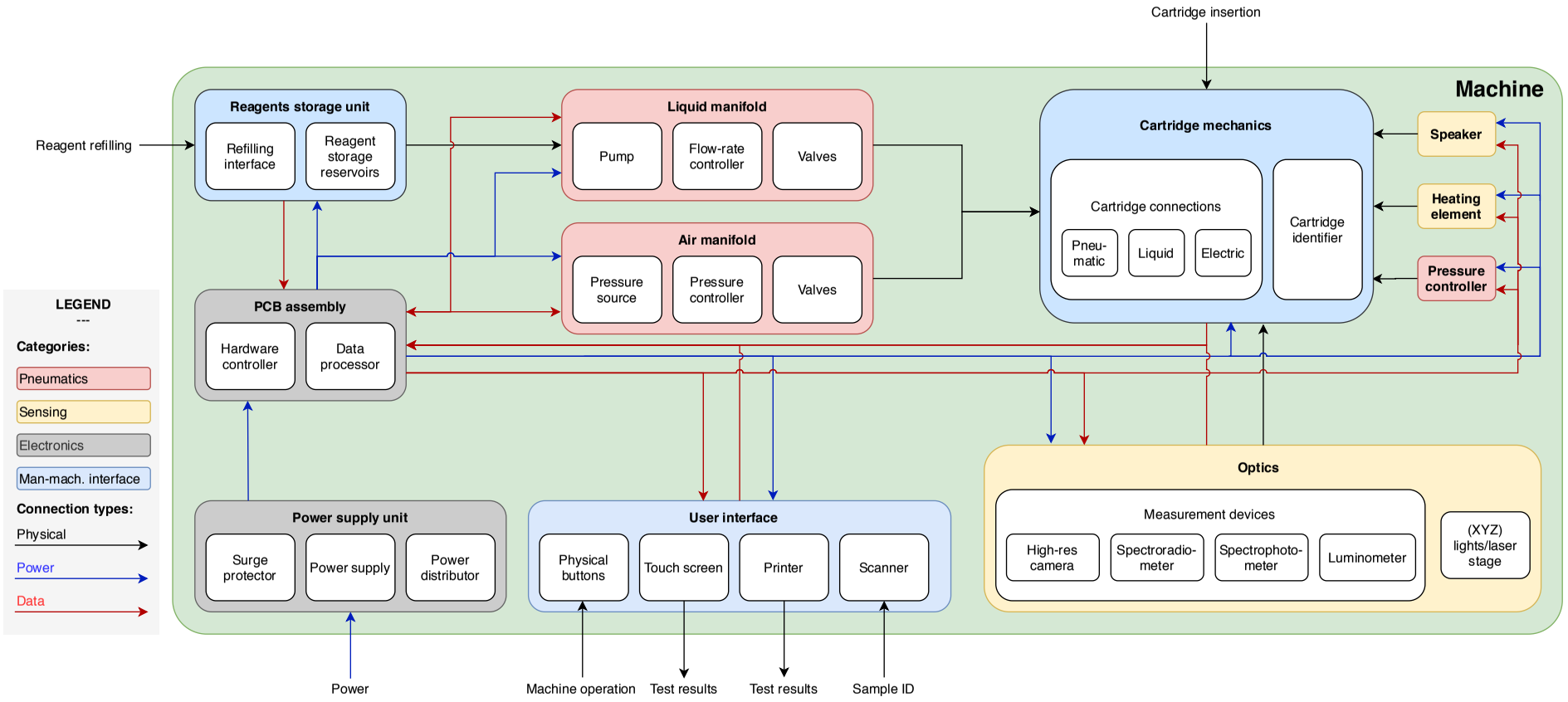


Figure 15. Improved system architecture diagram

3.4. Functional variant definition

Based on the research into the wishes of the two prominent use environments (POC, laboratory), it is clear these sufficiently differ to allow for the development of two functional variants of the microfluidics platform:

3.4.1. POC-variant

Optimize size, ease of use, and speed

The POC variant should be small and unobtrusive enough to fit in any point-of-care and primary care environment. Assay speed should be optimized and be fast enough for diagnosis while the patient is still in the clinic to allow for immediate decisions by the caregiver. This device should be catered to a carefully designed test selection, meaning chip-to-world connections and all required reagents are predefined.

Ease of use should be high, with minimal chance of human-error. Therefor the device should give clear step-by-step instructions on how to prepare the test-cartridge and change reagent reservoirs. Test procedure should be designed in such a way that human error is prevented.

The optics stage of the POC variant will only include a laser setup for spectroscopy analysis.

3.4.2. Laboratory-variant

Optimize sensing method variety, customizability, accuracy, and precision

Laboratories have very specific requirements for microfluidic platforms to conduct specific tests and observations. Therefor the device should accommodate for a broad variety of sensing methods, allowing the operator to cater the device to their needs. The same goes for fluid chip-to-world connections: the operator should be able to customise the reagent supply to the chip either by moving the connection points or exchanging reagent reservoirs.

There is also an extra need for ultra-sensitive measurement when compared to POC use. Laboratory use requires more accurate and precisely sensing techniques to accommodate to any type of chip and to properly carry out limitless types of medical and chemical analyses.

Chapter 4

Requirements specification

4.1. Introduction

This chapter presents the complete requirement set for both the POC-variant and the Laboratory-variant. First, a glossary is established, to concretize all specific terms in the requirement set. Next, the system states are defined. Then follows a textual description of the product, its users, operating environment, and operation procedure. Next, the requirement set for the POC-variant is presented, along with extra design guidelines. Finally, any additions to the POC-variant requirement set will be listed to define the requirements for the Laboratory-variant.

4.2. Glossary

To avoid ambiguity, terms used throughout the set of requirements are specifically defined here:

Device	Microfluidics analysis platform under design
Optics	All optical equipment necessary for detection and observation of on-chip behaviour, fluorescence, etc.
Filter	Light filter component necessary for fluorescence analysis
Analysis_Software	Software parts responsible for analysis of data gathered by the Optics
Speaker	Speaker subsystem
Heating_Element	Heating element subsystem
Air_Manifold	Air manifold subsystem
Liquid_Manifold	Liquid manifold subsystem
Pressure_Controller	Pressure controller subsystem
Power_Supply_Unit	Power supply unit subsystem
Cartridge_ Mechanics	Cartridge mechanics subsystem (includes all chip-to-world connections)
Liquid_Interface	Liquid chip-to-world interface
Pneumatic_ Interface	Pneumatic chip-to-world interface
Electrical_Interface	Electrical chip-to-world interface
Touchscreen	Touchscreen on the Device
User_Interface	Software user interface on the Touchscreen
Reagent_Reservoir	Reservoir for the storage one specific Reagent
Test_Cartridge	Cartridge with a pre-embedded a specific Chip for a specific medical assay
Cartridge	Cartridge without pre-embedded chip.
Reagent	Fluid to be used for on-chip reactions.
Chip	Microfluidics- or biochip

Time	Current time of day in either Time_Format with minute accuracy
Date	Current date in either Date_Format
Time_Format	Format of time: 24hr HH:MM or 12hr HH:MM
Date_Format	Format of date: MM/DD/YYYY or DD/MM/YYYY or YYYY/MM/DD
Reservoir_Interface	Man-to-machine interface for exchanging Reagent_ Reservoirs
Cartridge_Interface	Man-to-machine interface for inserting and extracting Test_Cartridges and Cartridges
Operator	Operator of the Device
Power_Switch	Physical interface on the Device to power on the Device
Cartridge_Identifier	Identifier of the type of cartridge and its Test_Type
Sample_Identifier	Identifier of the sample being tested
Instructions	Clear explanation on what actions to perform to transition to the next state
Storage_Level	Storage level of a Reagent_Reservoir, depicted in percentage format
Test_Type	Type of Test; specific parameter, medical assay, or test for disease
Test_Parameters	Duration of Test, necessary Reagents, sensing method, sample type, preparation steps, Filter type, Optics configuration, temperature, pressure, light wavelengths, sound frequencies, etc. – normally preconfigured based on Test_Type, but may be customised in the Laboratory-variant.
Test	Activity of carrying out a Test including all steps to go from sample to Test_Results (sample preparation, reagent dilution, sample actuation, excitement, measurement, results processing)
Reservoir_Warning	Warning to indicate one of the Reagent_Reservoirs is almost empty
Reservoir_Status	Filling percentage of specific Reagent_Reservoir (%)
Test_Progress	Progress of the test in percentages and expected time remaining
Test_Results	Quantitative results of the test
Error_Code	Error code and description if error occurs during a test

System states

OFF	The Device is turned off
STANDBY	The Device is turned on
PRE-TEST	The Device is preparing to run a test, ready to receive Test_Cartridge, Sample_Identifier, Test_Parameters etc.
TEST	The Device is running a test
POST-TEST	The Device is done with running the test and the results are displayed and can be exported.
REFILL	The Device is in refill modus, where the Reservoir_Interface can be accessed by the Operator so that the Reagent_ Reservoirs may be exchanged.
EDIT	The Device is in a modus where in a laboratory setting the Operator may edit the mechanics and Optics.

4.3. Overall description

The Device of concern performs medical assays from prefabricated Test_ Cartridges. Its use-scenario is the POC setting. The Operator shall be able to administer an untreated sample to the Device or Test_Cartridge, insert the Test_Cartridge, and perform a Test easily. The Device will carry out all necessary steps for the Test, including sample preparation, dilution, excitation, reagent mixing, reaction monitoring, data analysis. Results shall be displayed on screen, printed, or exported wirelessly via appropriate data-transfer protocols. Test time must be quick, so that the patient can wait while the test is being carried out. Time in-between tests must also be minimized.

4.3.1. Product features

The Device shall be suitable for use upon a table-top in an office or operating room setting. The most important features are the Touchscreen, Cartridge_ Interface, and Reagents_Interface. Via the Touchscreen, the Operator can interact with the Device to change settings, enter the ‘REFILL’ state, and perform tests. The Reagents_Interface is where the Operator can exchange Reagent_Reservoirs, to restock the Reagents. Lastly, the Operator can insert Test_Cartridges to the Cartridge_Interface, in order to facilitate testing.

Users

In the POC situation the primary users consist of GPs, doctors, physician assistants, and other medical personnel. While these users are generally trained for simple medical procedures, the Device should display clear Instructions for optimal use.

Operating environment

The POC-variant shall be used mainly in the primary care office, however it may also see use in secondary POC situations, like the operating room or ICU. In any case, the Device should be optimised for tabletop usage, and be not too large.

General operation procedure

The general procedure to carry out a Test is as follows:

1. The Operator turns the Device to the 'STANDBY' state with the Power_Switch and indicates in the User_Interface to start a test. The Device transitions to the 'PRE-TEST' state and Cartridge_Interface opens.
2. The Operator now follows the Instructions to input the Sample_Identifier into the Device, and place an unprepared sample (can be blood, throat swab, urine, depending on Test_Type) onto the Test_Cartridge. The Operator then places the Test_Cartridge into the Cartridge_Interface.
3. The Cartridge_Interface immediately reads the Cartridge_Identifier and displays the Test_Type and Sample_Identifier. The Device prompts to enter the 'REFILL' state if needed, and otherwise displays an option to start the Test.
4. When the Operator inputs to start the Test, the Cartridge_Interface closes and the Test commences. The User_Interface displays the Test_Progress as the test is carried out.
5. When finished, the User_Interface displays the Test_Results and give options to print or export the Test_Results, and an option to proceed to the next Test.
6. The Cartridge_Interface opens again allowing the Operator to extract and discard the Test_Cartridge. Simultaneously upon opening the Cartridge_Interface, the Device starts its internal cleaning and reset mechanism.
7. When the Operator selects to proceed to the next Test, the Device finishes its cleaning and reset procedure before transitioning back to the 'STANDBY' state.

4.4. Requirements

Here, the requirements of the device are listed in accordance with ISO/IEC/IEEE 29148-2018, as described by the INCOSE Systems Engineering Handbook [57] [58]. The goal of this requirement set is to be unambiguous, verifiable, and feasible.

4.4.1. Functional (F)

F1	When not in the 'OFF' state, the Device shall measure the Storage_Level of each Reagent_Reservoir.
F2	When not in the 'OFF' state, the Touchscreen shall display the User_Interface.
F3	The Cartridge_Interface shall read Cartridge_Identifier.
F4	When in the 'TEST' state, Cartridge_Mechanics shall establish any number of [Liquid_Interfaces] AND/OR [Pneumatic_Interfaces] AND/OR [Electrical_Interfaces] with the Chip, depending on the Test_Type.
F5	When in the 'TEST' state, the Optics shall observe the chip.
F6	When in the 'TEST' state, the Analysis_Software shall analyse data gathered by the Optics.
F7	The Device shall be capable of fluorescence spectroscopy.
F8	When in the 'TEST' state, the Heating_Element shall keep the Chip at the required temperature, based on Test_Type, within 5 degree Celsius*.
F9	When in the 'TEST' state, the Pressure_Controller shall keep the Chip at the required pressure within 5 bar*.
F10	When in the 'TEST' state, the Speaker shall play sound at a specific frequency within 5 Hz* at the chip.
F11	When in the 'TEST' state, the Liquid_Manifold shall supply each Liquid_Interface with the correct Reagent within a margin of 1 picolitre*.
F12	When in the 'TEST' state, the Air_Manifold shall supply each Pneumatic_Interface with a specific pressure within a margin of 5 bar*.
F13	The Device shall measure Test_Results with an accuracy greater than 99%.
F14	The Device shall store the Reagent_Reservoirs necessary for each Test_Type.
F15	The Device shall be able to output Test_Results to an SD-card, in the form of a PDF.
F16	The Device shall be able to output Test_Results wirelessly in accordance with the [POCT1-A] AND [HL7] AND [ASTM E1394] AND [LIS2-A2] protocols.[a]

[a] *Based on industry state of the art*
** the basis of these values are beyond the scope of this project, which means these may change in the future*

4.4.2. Non-functional (NF)

NF1	A Test shall take less than fifteen minutes, depending on Test_Type.
NF2	The Device shall fit within a 300mm cubed box of space.[b]
NF3	The Device shall be ready to accept a new Test_Cartridge within less than one minute after exiting the 'POST-TEST' state.

[b] *Based on the length of the long edge of an A3, in combination with the wish to have the device be for use on a tabletop.*

4.4.3. State Transitions (ST)

ST1	When in the 'OFF' state, the Power_Switch shall change the Device to the 'STANDBY' state.
ST2	When in the 'STANDBY' state, the Power_Switch shall change the Device to the 'OFF' state.
ST3	When in the 'PRE-TEST' state, the Device shall enter the 'REFILL' state, when [the Storage_Level of a Reagent_Reservoir is less than 10%] AND [that same Reagent_Reservoir is required for the Test_Type].
ST4	When in the 'PRE-TEST' state, the User_Interface shall display an option to enter the 'TEST' state.
ST5	When in the 'POST-TEST' state, the User_Interface shall display an option to return to the 'STANDBY' state.
ST6	When in the 'REFILL' state, the User_Interface shall display an option to return either the ['PRE-TEST'] or ['STANDBY'] state.

4.4.4. Man-Machine Interfaces (MM)

MM1	When not in the 'OFF' state, the Operator shall be able to interact with the User_Interface via the Touchscreen.
MM2	The User_Interface shall display the [Time] AND [Date].
MM3	When in the 'STANDBY' state, the Operator shall be able to input the Sample_Identifier.
MM4	When in the 'STANDBY' state, the User_Interface shall display an option to enter the 'REFILL' state.
MM5	When in the 'STANDBY' state, the User_Interface shall display an option change the [TIME] AND [DATE].
MM6	When in the 'STANDBY' state, the User_Interface shall display Reservoir_Warning, when any one Storage_Level is below 25%.
MM7	When in the 'STANDBY' state, the User_Interface shall display Instructions to input Sample_Identifier.
MM8	When in the 'PRE-TEST' state, the User_Interface shall display the [Sample_Identifier] AND [Test_Type based on the Cartridge_ Identifier]

MM9	When in the ‘PRE-TEST’ state, the User_Interface shall display Instructions based on the Test_Type.
MM10	When in the ‘TEST’ state, the User_Interface shall display the Test_Progress.
MM11	When in the ‘TEST’ state, the User_Interface shall display the Error_Code if an error occurs.
MM12	When in the ‘POST-TEST’ state, the User-Interface shall display Test_Results.
MM13	When in the ‘POST-TEST’ state, the User-Interface shall display an option to export Test_Results.
MM14	When in the ‘POST-TEST’ state, the User_Interface shall display Instructions to discard the used Test_Cartridge.
MM15	When in the ‘REFILL’ state, the User Interface shall display the Storage_Level of each Reagent_Reservoir.
MM16	When in the ‘REFILL’ state, the User_Interface shall display Instructions to exchange each empty Reagent_Reservoir.
MM17	When in the ‘OFF’ state, the [Reservoir_Interface] AND [Cartridge_Interface] shall be inaccessible to the Operator.
MM18	When in the ‘STANDBY’ state, the [Reservoir_Interface] AND [Cartridge_Interface] shall be inaccessible to the Operator.
MM19	When in the ‘PRE-TEST’ state, the Cartridge_Interface shall be accessible to the Operator.
MM20	When in the ‘PRE-TEST’ state, the Reservoir_Interface shall be inaccessible to the Operator.
MM21	When in the ‘TEST’ state, the [Reservoir_Interface] AND [Cartridge_Interface] shall be inaccessible to the Operator.
MM22	When in the ‘POST-TEST’ state, the Cartridge_Interface shall be accessible to the Operator.
MM23	When in the ‘REFILL’ state, the Reservoir_Interface shall be accessible to the Operator.

4.4.5. Safety (S)

S1	In the event of a power cut or power outage, the Power_Supply_Unit shall provide emergency power to the Device for a minimum of one hour.
S2	The Device shall clean Cartridge_Mechanics between tests.
S3	The Cartridge_Interface shall accept only one Test-Cartridge at a time.[c]
S4	The Device shall evaluate Test_Results based on calibration to avoid error.

[c] *Based on test time, to not corrupt data or results.*

4.5. Guidelines

Not all wishes can be defined as unambiguous, verifiable requirements. Instead, these are translated into design guidelines. These may serve as holistic guidelines for the design process and should always be kept in mind.

1	The physical appearance of the Device should convey robustness and reliability.
2	The physical appearance of the Device should be fitting in a medical environment.
3	The User_Interface should be self-explanatory and usable by the Operator without major additional training
4	Performing a test should be easy and require minimal operating steps.
5	The design of the Device should not obstruct cleaning and sterilization.
6	The design of the Device should allow for repairs of the internal mechanism.
7	The physical dimensions of the device should be fitting for the use-environment (while also adhering to **NF2**).
8	The amount of moving parts in the construction of the Device should be minimised.
9	Test results should be delivered in a straightforward manner without room for confusion or misinterpretation.

4.6. Additions and changes for the Laboratory-variant

This section addresses any additions or changes for the Laboratory-variant. Strikethrough entries were valid for the POC-variant, but no longer relevant for the laboratory-variant.

4.6.1. Functional (F)

F17	The Device shall be able to output Test_Results to software on an external computer.
F18	The Device shall be capable of recording activity on the Test_Chip with a microscopic camera.
F19	The Device shall be capable to export data gathered during a Test.

4.6.2. Non-functional (NF)

~~**NF1**~~	~~A Test shall take less than fifteen minutes, depending on Test_Type.~~

4.6.3. State Transitions (ST)

ST7	When in the 'PRE-TEST' state, the User_Interface shall display an option to enter the 'EDIT' state.

4.6.4. Man-Machine Interfaces (MM)

~~**MM9**~~	~~When in the 'PRE-TEST' state, the User_Interface shall display the [Sample_Identifier] AND [Test_Type based on the Cartridge_Identifier]~~
MM25	When in the 'PRE-TEST' state, the Operator shall be able to input custom Test_Parameters.
MM26	When in the 'PRE-TEST' state, the User_Interface shall display the [Sample_Identifier] AND [Test_Type].
MM27	When in the 'REFILL' state, the Operator shall be able to input custom Regents to the Reservoir_Interface.
MM28	When in the 'TEST' state, the User_Interface shall display the data gathered by Optics in real-time.
MM29	When in the 'EDIT' state, the Optics shall be accessible by the Operator.
MM30	When in the 'EDIT' state, the Operator shall be able to change the Filter.
MM31	When in the 'EDIT' state, the User_Interface shall display an option to return to the 'PRE-TEST' state.

4.6.5. Safety (S)

	No additions

Chapter 5

Designing the platform

5.1. Introduction

This chapter documents the design process of the microfluidic platform. First, conclusions are presented from literature describing points of attention when designing for the medical space. Next, before any ideation was done, size requirements of components within the device (e.g. size of the optic sensing electronics) are presented, to keep in mind when sketching concepts. Then, the various user interactions are listed with options presented for each in several morphological charts.

Ideation and inspiration collages are presented to find a design direction for the device. Following, this chapter documents all ideation sketches that led to the final design. The ideas diverge into three directions, and of each direction two concepts are worked out into neat renders. Finally, it was chosen to combine two good concepts to form the final iteration. Based on this, the final design is presented in chapter 7.

5.2. Designing for the medical space

In the development of medical products, the key drivers usually consist of safety, efficiency, and quality. This means design takes the backstage, often resulting in suboptimal user experience, and an overall more negative emotional experience. Good design is paramount to create a good product, and thus the visual characteristics and user-interactions need special attention.

Before designing a device for the medical industry, it is necessary to investigate best practices and the status quo of the medical space. This will give insights into what medical staff are familiar with. Furthermore, the appearance of the device and its aesthetics should match the operators' expectations and the design should elicit a feeling of sophistication.

In a previous bachelor thesis for Benchmark, Huong Nguyen analysed the implications of the design of a medical device on emotion and user experience [59]. Furthermore, an excellent interview with Bartosz Korec, lead industrial designer for BlackHägen Design, introduces some important points of attention when designing for the medical space.

The BlackHägen Design studio is responsible for various medical product designs for Philips, Abiomed, GE Healthcare, Medtronic, and more. The next sections outline Nguyen's and Korec's perspectives.

5.2.1. Guideline by Huong Nguyen

In a previous bachelor thesis for Benchmark to investigate the emotion-driven design guidelines for medical products, Huong Nguyen compiled a good guideline for design [59]. Here the most relevant points concluded by Nguyen's research are listed.

The general rules for aesthetic appeal conclude that ideally the design of the product should include symmetry, rounded edges, and polished surfaces. According to Nguyen, people tend to associate simple, sleek forms with sophistication and a feeling of high technology. Next, regarding colour, Nguyen concludes common colours in the medical world are white, for its association with sterility, grey as a less intrusive substitution for white, and black to convey richness and sophistication. These colours are ideally paired with either blue or (slightly less commonly) green, as both are associated with healthcare and convey calmness and strength. Red should be reserved for important attention-grabbing mechanisms.

Regarding usability, of course, the important functions of the device (e.g. power button or switches) should be obvious, and the variety of inputs limited, as to not overwhelm the user. This is especially important in stressful situations such as the POC.

Nguyen also states the very important requirement that the device should ideally be portable, since the POC sees many patients. It is likely that medical staff will have to move the device to other patients frequently. Thus, the device should not be too large, easy to carry, and without sharp or potentially hazardous edges.

It is clear the designer must find the correct balance between utility and trend. While the key drivers remain safety, efficiency, and quality, a good design can improve the patient and caregiver experience.

5.2.2. Interview with Bartosz Korec

The clinician's needs can be quite different from the patient's, but their first and foremost concern is efficiency, intuitiveness, and reduced errors during operation. According to Korec, to avoid accidental misuse the product's operation

must be clear and instinctive. The device should be designed in such a way that safe operation is possible without the need for extensive retraining, as medical staff often lack the time for this. Where possible, the device should guide the user in its operation. However, these guided procedures should not slow down an experienced user, especially in the field or during stressful, time-critical situations.

Next, Korec states alarm design is critical to patient safety. He explains an important selection needs to be made between critical and non-critical alarms, to minimize clinical staff overstimulation. Of course, this is also very important at the bedside, as the patient will be noticing the alarm too. Auditory and visual cues should never upset the patient or cause extra stress.

The operating room is a very specific environment with its own design requirements. Korec states one must pay special attention to the design of the user interface here, since emitted light might disrupt procedures in a darkened lab; sometimes “reverse GUIs with black backgrounds are more suitable”. Next, one must ensure devices are operable in the dark, and in slippery environments (e.g. blood, fat). Operating the device should also never compromise the clinicians’ personal protective equipment like latex gloves.

Another very important requirement relates to device maintenance and hygiene. Consoles and equipment are cleaned very regularly to ensure patient safety and lower the risk of contaminations. Korec advices to keep this in mind during the design process and avoid creating “dirt traps like recesses and crevices” or other parts that might be difficult to reach for cleaning. One must also carefully consider the use of touchscreens as an alternative to knobs and buttons to solve this.

5.3. Existing devices

Since Benchmark is not traditionally an OEM, but rather provides EMS, there are no established brand design guidelines. Thus, instead of looking at Benchmark's portfolio of products, here several designs in the existing POC market are investigated. This will establish the status quo of medical device aesthetics and design, so we can build further upon it.

The design of existing POC devices ranges from outdated-looking and bulky to fresh and modern. Important factors to give the design its 'freshness' are overall size of the device, and design of the graphical GUI. Along with this, colour selection is very important; 'cleaner' and more vibrant colours generally express modernity. Consider the following comparison between a beige/blue and a black/white (Photoshopped) Alere Afinion 2 in figure 16. The black and white version looks noticeably more modern than the blue low-contrast model. It offers other advantages too, such as the possibility to have a flush touch-screen on a black opaque glass panel.

Figure 16. Comparison between beige/blue and a black/white Alere Afinion 2 (images taken from Abbott [40])

Next, consider the GNA Neo and Helios in figure 17. Both devices are adherent to one consistent style, featuring white and dark grey as main colours, smooth simple surfaces, and friendly rounded edges. Noticeable is that primary man-machine-interfaces adhere to the grey colouring, while any excess is white. The screens feature rounded colours and resemble modern smartphones. Special consideration has gone into the GUI, which is modern, usable, and minimal, again resembling modern smartphone applications.

Figure 17. GNA Neo and GNA Helios (images taken from GNA BioSolutions from [60])

More prominent existing molecular diagnostics devices are shown in the collage in figure 18. It is clear widely used colours are white and black/dark-grey, while the accent colour is usually blue. Common are touchscreens with modern smartphone-like GUIs and data exports to a companion application (mobile device or computer). Only the Piccolo Xpress has an embedded printer. Inputs to the devices are virtually always cartridges.

Figure 18. Existing POC devices

5.4. Size requirements for the device

The platform has certain mechanical and functional requirements that influence the design. For instance, to perform spectroscopy analysis, a complex laser and filter stage is necessary. While this and other components will be regarded as 'black boxes', they have unavoidable requirements for size and shape. The dimensions indicated here are approximations to guide the design process.

5.4.1. Cartridge mechanics

All pneumatic and sensing subsystems need direct contact with the microfluidic chip that is embedded in the cartridge. This means the cartridge, when inserted into the machine, will be sandwiched between chip-to-world interfaces on one side, and optical analysis components on the other.

- The white box in figure 19 represents the cartridge with dimensions 100x70x10 mm.
- The green box in figure 19 represents the laser, detector, and filter stage. Volume for this differs between the POC and laboratory variants. As a guideline, the POC variant shall have a maximum height of 180 mm. Likely the high will become less if components are spread out more over the width, or if the section incorporates a corner.
- The speaker, heating element, and pressure controller are also embedded in the green box.
- The purple box represents all chip-to-world connections for fluid, gas, and electricity. As a guideline, it shall measure 90x60x100 mm.

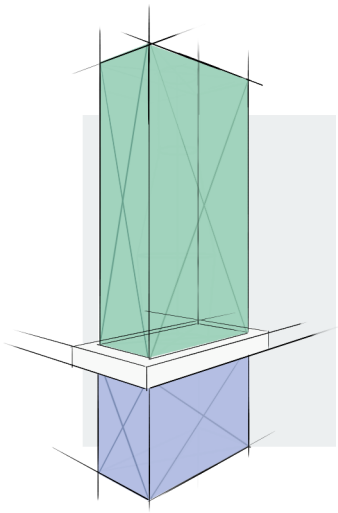


Figure 19. Black boxes representation

5.4.2. Reagent storage

The device will need to hold at least ten reagent storage vials, each holding 1.5 mL. Commonly, reagent vials have a dimension of 10x40mm (cylindrical, see figure 20). A mechanism to connect these vials to the liquid manifold should also be in place, adding volume to the whole reagent storage assembly.

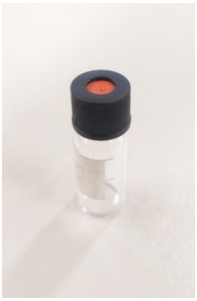


Figure 20. Reagent reservoir

5.4.3. Electronics and manifolds

Necessary are a PSU, PCB assembly, pumps, valves, liquid manifold, and air manifold. These components will fill the rest of the device; however, we must keep in mind airflow for cooling.

5.5. User interactions overview

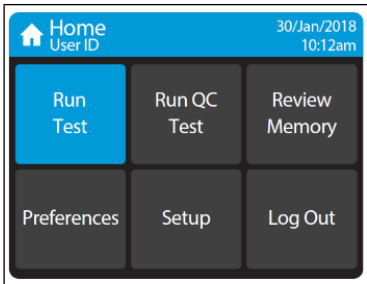
The next section highlights which user interactions need to be designed into the device, and various options thereof. These are later combined in a morphological chart.

5.5.1. Interacting with the GUI

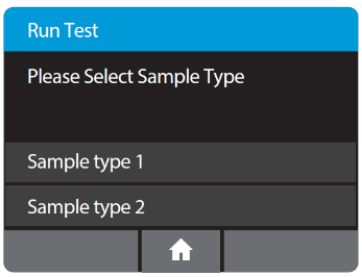
As stated in the requirements specification, the operator will need to interact with the machine via the GUI to transition between the various machine states, and to input and read relevant information. For this, user experience design is of prime importance, as to improve user flow, operating speed, and reduce human error. Modern existing devices mostly adhere to a minimalistic GUI, which reduces the error chance. The GUIs of the Abbott ID-NOW and Abionic's AbioSCOPE are shown in table 7 and table 8, respectively.

It is important to note that the size of the display is of particular interest, since the input of patient ID may require numeric or alphanumeric input (based on practice preference), thus exhibiting the need for a full alphanumeric keyboard. This is something where the Abbott ID-NOW struggles, since the screen is only approximately 5 cm in width. In contrast to the ID-NOW, Abionic's AbioSCOPE offers a large screen, which enables quicker patient input, and thus faster operation. Furthermore, the AbioSCOPE's user interface is more streamlined, since there are only two main buttons present, at any given time.

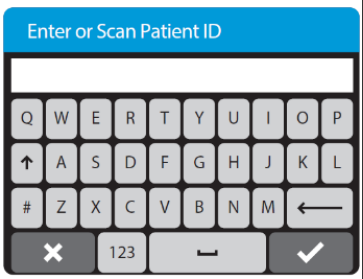
Table 7. Abbott ID-NOW home-screen, test selection, and patient ID screen (image taken from ID NOW user manual [37])



1. Home screen



2. Select pre-configured sample type and test type

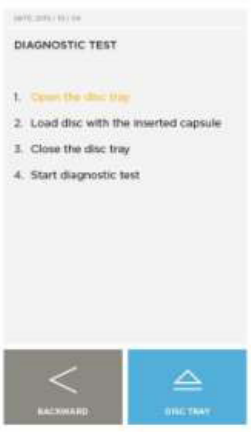


3. Enter patient ID

Table 8. Abionic AbioSCOPE diagnostic test workflow (images taken from AbioSCOPE User Manual [47])

1. Home-screen

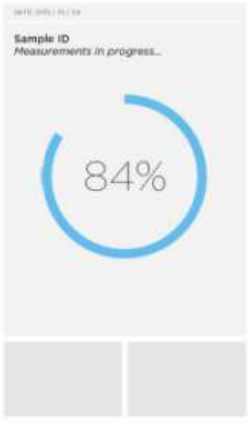
2. Input patient parameters



3. Test instructions

4. Insert disc

5. Start sequence



6. Test progress

7. Read results on-screen

8. Or export to companion app via QR-code

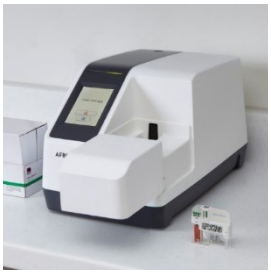
5.5.2. Recommendation

What is best is a simple, minimalistic GUI that is streamlined to perform the most frequently operations. The screen should be large, and with a high contrast ratio, as to improve readability. GUI buttons should have a large trigger-area, to increase operation speed. Doing a test should be made easy, without the need to manually input test type. Instead, the device should read this from the cartridge automatically. Furthermore, exporting of data should not require complicated extra steps for the user, such as scanning a QR-code through a companion application. Instead, the device should be connected to the practice's intranet and optionally an external printer.

5.5.3. Inserting and extracting the cartridge

It is paramount that the user makes no mistake when inserting the cartridge. Current methods for cartridge mechanics include slides that come out of the machine, lids that open to reveal the cartridge position, and slots to push the cartridge into. The three options are listed in table 9 below.

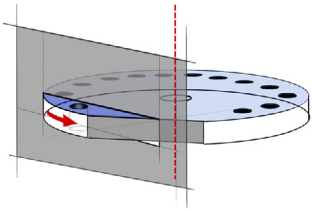
Table 9. Cartridge mechanics options

		
1. Slide that comes out of the machine	**2. Slot to push cartridge into**	**3. Lid to reveal position**
+ Only one way to insert cartridge + Flush when not in use + Familiar principle (CD-drive)	+ Works for any cartridge size + Familiar principle	+ Clear how to insert cartridge + Flush when not in use
- Strictly motorised operation - Lacking structural integrity for large cartridges - Works only horizontally	- unclear cartridge orientation - requires user to push or motors to latch onto cartridge	- Strictly motorised operation - Large moving part - Decreased structural integrity

5.5.4. Replacing reagent reservoirs

Current existing cartridge-based analysis devices all store the required reagents on-cartridge. This means a reagent storage mechanism inside the device is not required. In contrast, our device will store the reagents inside of the machine. This means an intuitive interface needs to be designed, to replace or refill the reagent reservoirs. In table 10 below, three viable options are listed.

Table 10. Reagent interface options

		
1. Slide that comes out of machine	**2. Angled cover**	**3. Rotary mechanism**
+ Familiar principle + Multiple reagents accessible at a time + Multiple rows and columns	+ Familiar principle + Multiple reagents accessible at a time	+ Only one reagent at a time; no confusion
- Large moving part - Long distance between reagent reservoirs and cartridge mechanics	- relatively poor usability	- large moving part - Only one reagent at a time; slower operation - Very complex mechanics

5.5.5. Customising optical stage

The laboratory variant has as additional requirement that the components of the optical/sensing stage may be switched out and customised by the user. This means the device requires an additional opening which gives access to these internal mechanisms.

The best option here is creating a hinge mechanism so the user can open part of the device casing, as illustrated by figure 21. Naturally, this removable cover should then give access to the optics part of the mechanism.

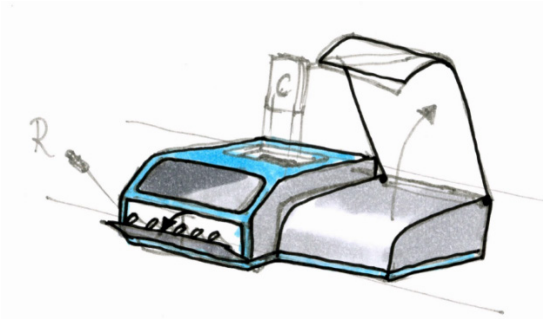


Figure 21. Opening part of the device casing to access internals

5.6. Idea generation

Along with the collage of existing devices, creating inspirational collages (figure 22) helped define a direction for the aesthetics and detailing. The clean sweeping lines separating white and black surfaces give the products a modern appearance. Figure 23 shows initial ideation sketches.

Figure 22. Inspirational collage

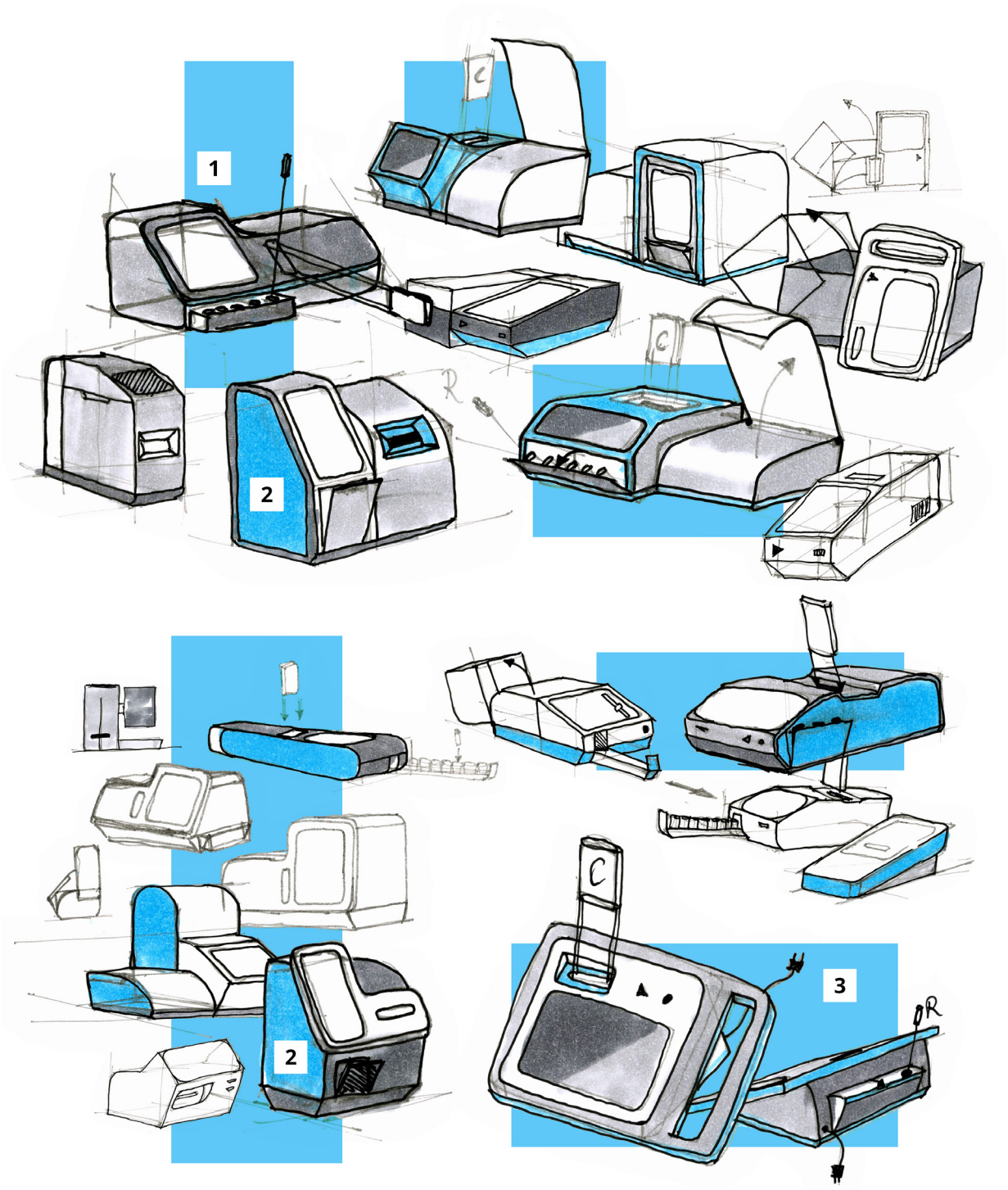


Figure 23. Ideation sketches (numbers indicate design directions)

Three design directions were established based on the orientation and layout of the internal components. Mainly the sensing column and cartridge mechanics played a large part in this. As shown in figure 24, the three orientations consist of 1) horizontal sensing column parallel to the table edge, 2) vertical sensing column, 3) horizontal sensing column perpendicular to the table edge.

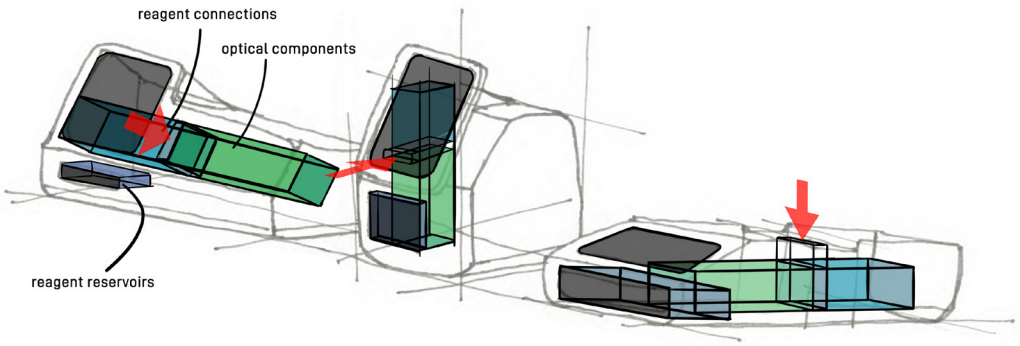


Figure 24. Three design directions component layouts

Red arrows indicate cartridge insertion point

Based on the three component layouts, further iteration was done. The results are compiled in figures 25-27.

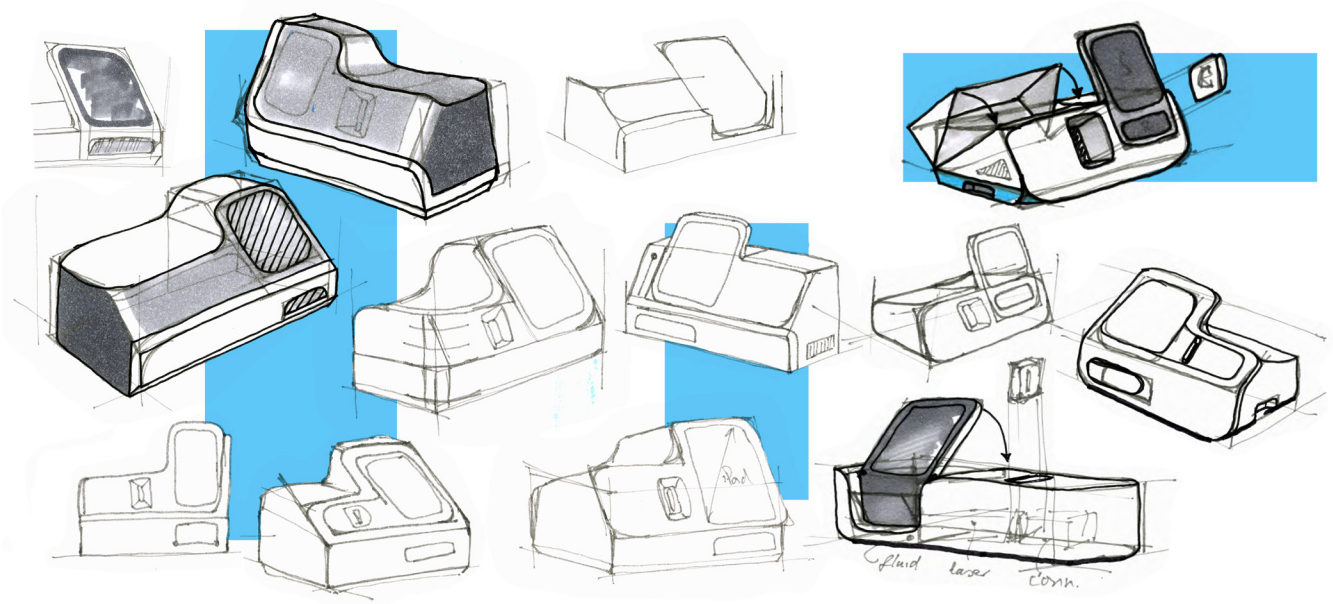


Figure 25. Iterations on direction 1

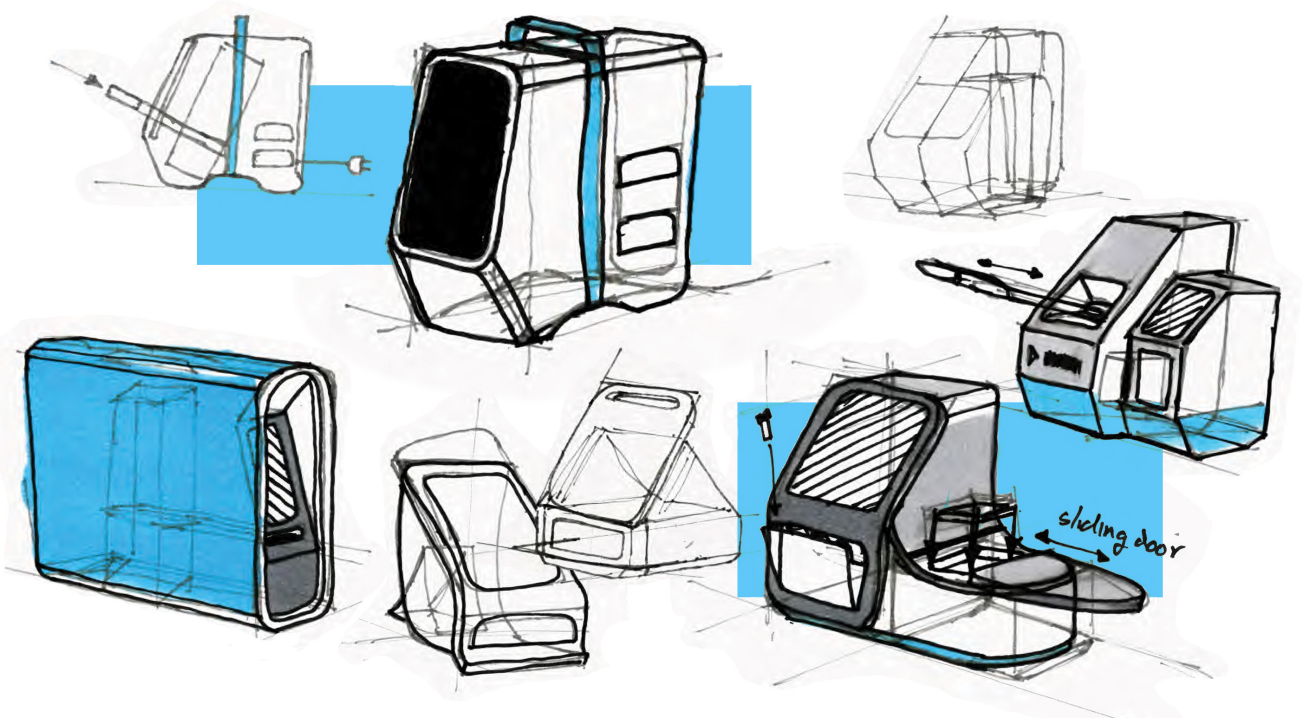


Figure 26. Iterations on direction 2

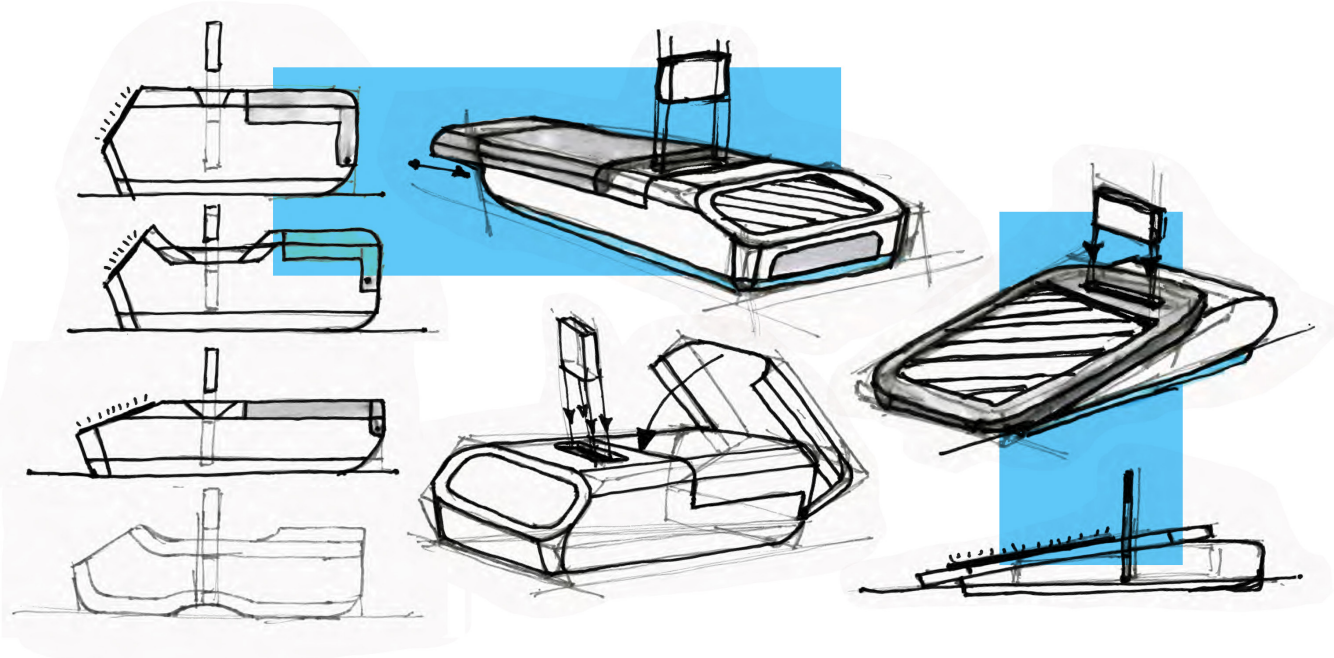


Figure 27. Iterations on direction 3

Two concepts were rendered for each component layout direction (figure 28-30). While the below renders are quick and dirty, they do properly convey the explored design directions. Depicted every time is the POC variant, which means all core functions are thought of (reagent storage, cartridge mechanics, touchscreen, sensing). The designs will need to be altered and expanded upon to facilitate laboratory functions or be suitable for portable use. In these renders, the GUI shown on the touchscreen is a placeholder.

Version 1.a **Version 1.b**

Figure 28. Quick iteration renders direction 1

Version 2.a **Version 2.b**

Figure 29. Quick iteration renders direction 2

Version 3.a Version 3.b

Figure 30. Quick iteration renders direction 3

5.7. Concept selection

As the requirements specification was drafted before starting the ideation process, it was kept in mind continually. As such, all the concepts adhere to the requirements, with only minute deviations. Thus, the requirements specification is not suitable as a ground for concept selection. Instead, selection will be based on the guidelines as listed in chapter 4.6 and gut feeling.

Considering this, version 1.a is too bulky and does not convey properly 'sterile sophisticated medical device'. Version 2.b is too bulky and opts for suboptimal cartridge insertion on the side of the device, thus neglecting its quality of a thin footprint. Version 3.a simply looks unappealing. The design of version 3.b is appealing due to the glossy black interface panel facing the user and the incorporated carrying handle. However, it does not properly consider the size requirements of the sensing and cartridge mechanics, nor does in incorporate an ergonomic reagent storage unit. Version 1.b and 2.a were chosen as concepts and are elaborated upon below.

5.7.1. Version 1.b

Combining a glossy white plastic body, smooth lines, and a black reflective user-interface gives this design (figure 31) a modern and sophisticated look. The screen is large and faces the user under a pleasant angle when the device is placed on a table or countertop. The cartridge is inserted from the front.

This design can be easily altered to fit in a portable rugged package, furthermore there is enough space to expand sideways for more sophisticated sensing equipment for the laboratory-variant. For the laboratory use-case, the backside of the device could incorporate a door to access the internals to swap out filter or other crucial components.

Currently, the reagent storage unit is unaccounted for. Furthermore, the pleasant light blue accent colour is missing from the design. Further iteration is required.

Figure 31. Version 1.b

+ design
+ expandability
+ suitable for portable
- lacking light blue accent
- wide footprint
- no reagent storage unit

5.7.2. Version 2.a

In terms of design language this version is very close to 1b. Again, the combination of glossy white with reflective black is very familiar within the medical space. In contrast with 1.b, the computer-case form factor lends itself more to desktop usage, or other applications where the width of the footprint needs to be reduced. See figure 32 for a render.

Like 1.b, this design also features a large screen placed on an optimal angle. The cartridge is inserted in the front. However, the current render shows reagent storage on the side of the machine, which is suboptimal in terms of ergonomics. Next, this variant lends itself less to alteration into a rugged portable version, thus requiring further iteration.

On the other hand, this variant is very suitable for laboratory-use, since it is large enough to house more sophisticated mechanisms without expanding the body.

Figure 32. Version 2.a

+ design
+ size/footprint
+ suitable for laboratory
- unsuitable for portable
- unergonomic reagent storage unit
- looks like Bosch Vivalytic from the front

5.8. Concept iteration

The two concepts are good; however, each has a severe downside. Version 1.b takes up a lot of horizontal desktop space, whilst leaving the depth of the desk unused. The second concept does not have this problem. Instead, its criticism is that it looks too much like the Bosch Vivalytic from the front.

Based on these comments, it is clear the concepts could be combined into a superior design. The final should be larger in depth than width, as to optimally occupy the desktop. Next, its front silhouette should differ from the Vivalytic. Iteration sketches are shown in figure 33 and 34.

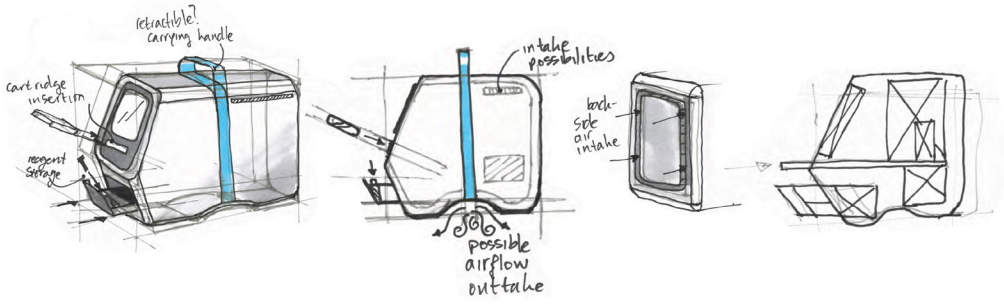


Figure 33. Iteration on concept version 2.a

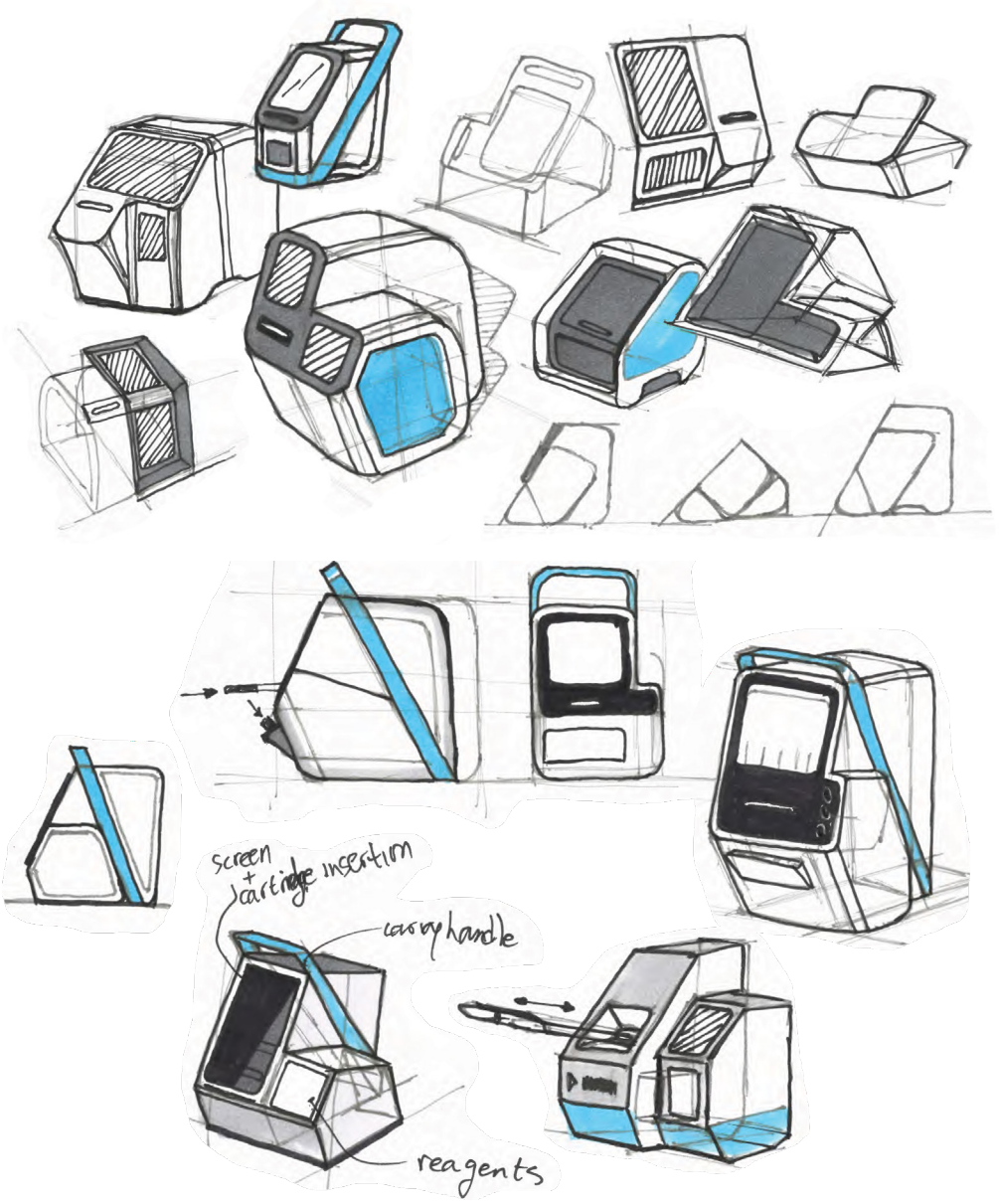


Figure 34. Iteration towards final concept

The final concept should break up the silhouette by adding a volume to the side of the main device body. On the front, this is where hardware/capacitive buttons are be placed. The carrying handle will also be incorporated into the design. The first idea for the final design is shown in figure 35.

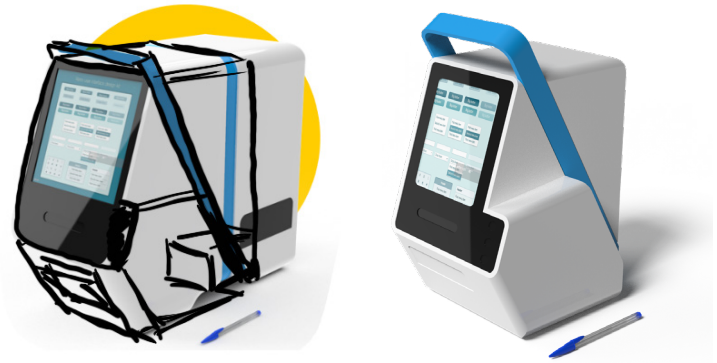


Figure 35. First idea of final concept based on render 2.a

5.9. Final iteration

The final design iteration stays close to concept 2.a's good proportions, and the sleek carry handle. The carry handle extends past the added volume on the side of the device. The outcrop on the bottom adds another ergonomic hand placement on the bottom left of the device.

Both the reagent storage hinge, cartridge mechanics, and the display are on the front of the device, with capacitive buttons embedded in the black glass. These buttons will allow the user to quickly access frequently used functions without navigating the software.

The volume of the device should be kept as small as possible. Therefor the pen in figure 36 serves as a size indication and should be the aim.

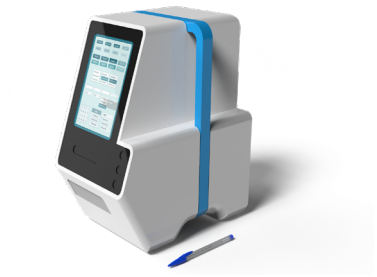


Figure 36. Final iteration step

Chapter 6

Usability analysis

6.1. Introduction

This chapter presents a small and preliminary usability analysis based on a physical model and a GUI mock-up. While a GUI was initially not part of the design brief and assignment description, it was deemed necessary to test some of the user-interactions with the device.

First in this chapter, the physical model is introduced, showing the user-interactions and the way the device is intended to be held while carrying. Creating a prototype helped determine the scale and size of the digital model.

Next, three Benchmark employees were asked to go through a scenario to test the GUI and some simple interactions with the model. Each was asked to refill the reagents and perform a cartridge test. The results indicate some points of attention for creating the final design.

6.2. Physical model

A model of the device was made from foamboard and cardboard. This was an important step to properly assess size, scale, and proportions of the design. In fact, using the digital model as a direct reference yielded a device that was too small. Instead, the cardboard model was made 150% the size of the initial computer-aided-design (CAD) model. This gave a far more realistic result.

The model also aided in testing the ergonomics of the display, reagent cover, and carrying handle. The two front panels for the display and reagent cover are angled, and thus should be tested to make sure the angle fits for any operator of the device. Figure 37 shows the model and important user interactions (using capacitive buttons, inserting cartridge, changing reagents). Figure 38 shows the model being carried with the integrated carry handle and with the left hand placed in the recess on the bottom of the device.

This version of the device has three capacitive buttons on the front: 1) ‘ON’-button to turn the device on, standby, or off when held down, 2) ‘START TEST’-button to enter the test menu, and 3) ‘REAGENTS’-button to enter the reagent refilling menu.

Figure 37. Photos of the model and the important user interactions

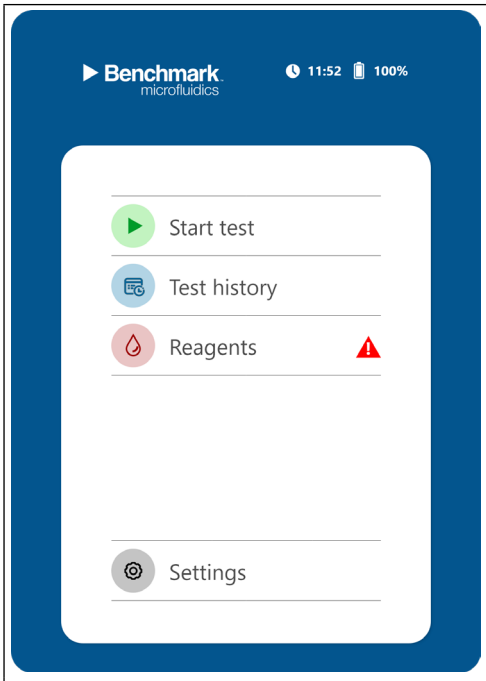
Figure 38. Photo showing the device being carried as intended

6.3. Interaction testing

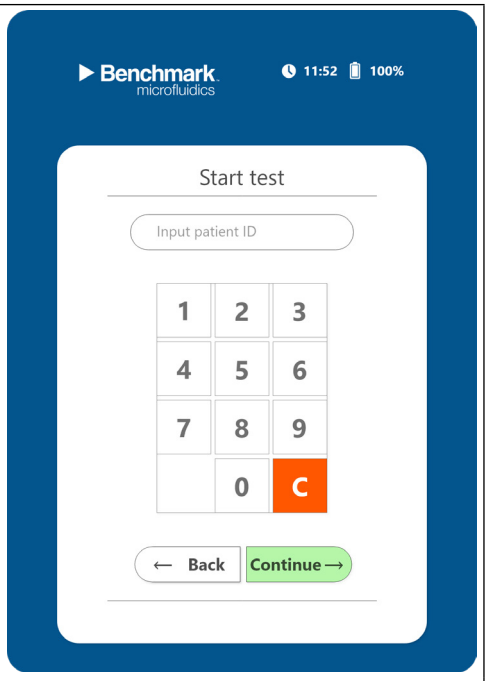
6.3.1. Graphical user interface mock-up

Because the device is largely reliant on software, user testing solely with this lo-fi prototype is impossible. The main interactions (inserting cartridge and exchanging reagents) are always supported by the user interface. Thus, to create the possibility of conducting a user test, a mock-up user interface was created to support carrying out a test and exchanging the reagents. See table 11 and figure 39 below for relevant GUI screens. The mock-up was made in Adobe XD and is partially functional.

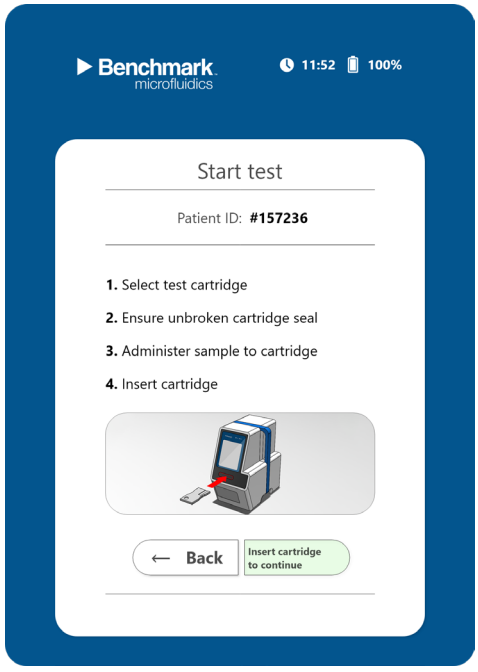
Table 11. Benchmark microfluidic diagnostic test workflow



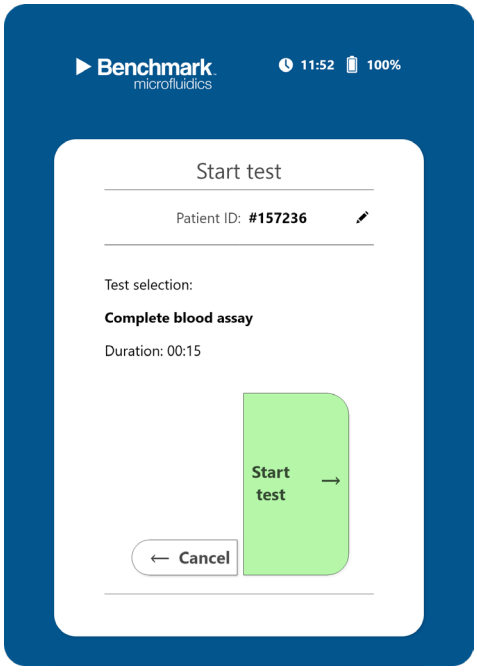
1. Home-screen with reagent warning



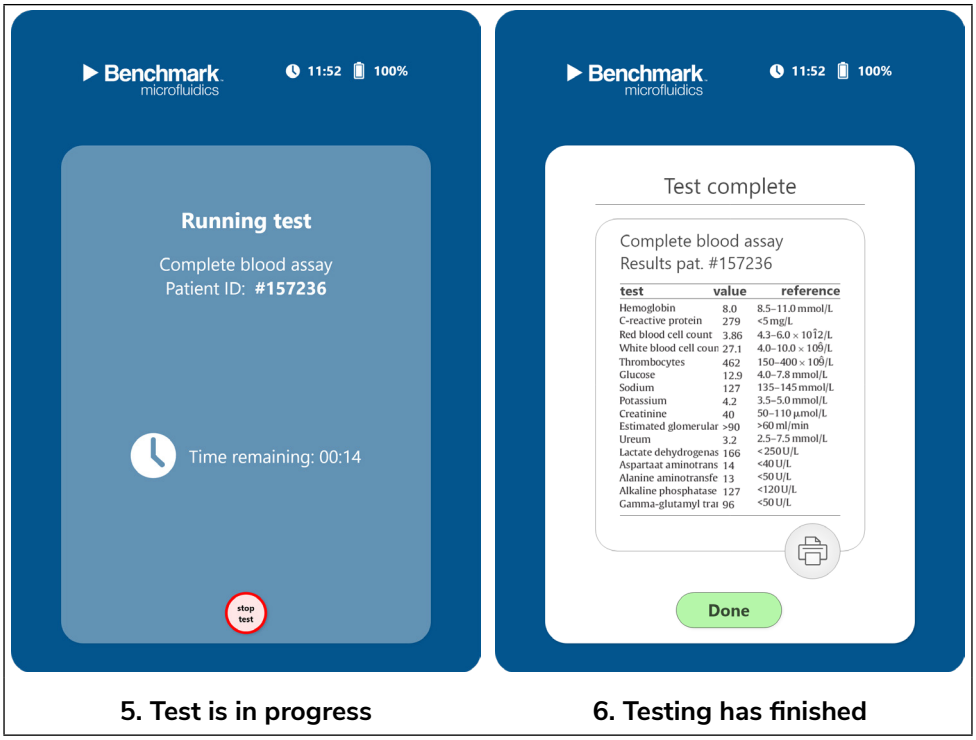
2. Inserting patient details when starting test



3. Instructions to insert cartridge



4. Cartridge test is recognised. Last confirm before test starts



5. Test is in progress 6. Testing has finished

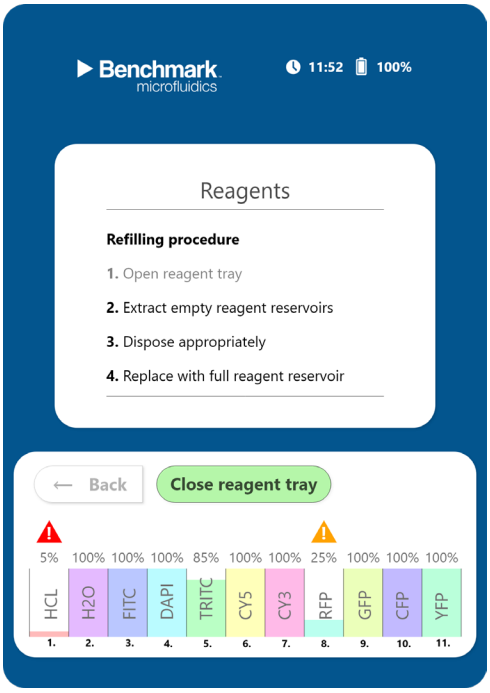


Figure 39. Reagents overview screen with refilling procedure

User test

To test the user interface and the affordances of the final design, three Benchmark employees (not involved with the project) were tasked to 'refill the reagents' and 'carry out a test'. For a full overview of the testing procedure, see annex 2.

In the test setup the GUI was shown on a computer screen to be interacted with by mouse. The model of the device was displayed next to the screen to serve as context. See figure 40 of a photograph of the test setup.

Figure 40. Photograph showing test setup

All three testers could navigate the GUI properly and were able to carry out a test without problems. Ergo the testing results were satisfactory. Refilling the reagents was more difficult: because the GUI was shown on a computer monitor instead of the device display, there was a disconnect between what was on screen and what was happing to the device (reagent tray opening/ closing).

The final device should reinforce the cause-effect relation between pressing the display button 'open reagent tray', and the physical tray opening. For this, an animation could be shown on screen. What is more, the connection between

the vertical alignment of the screen with the reagents (figure 41) should be reinforced.

Figure 41. Render showing reagents screen matching with physical reagents vertically (red lines)

Finally, it became clear from the user test that the device hosted too *many* capacitive buttons. Initially, they were intended to be an 'ON'-button, 'START TEST'-button, and 'REAGENTS'-button. However, this led to confusion since the system is unable to flow from any specific state to another. For instance, it is impossible to enter the reagents menu while the device is running a test. This created confusion since the button to enter the reagents menu stayed present throughout all device states. Thus, when running the test, the button was present and press-able, however without effect.

What is more favourable was to keep only a single capacitive button, serving as the 'ON'-button (turning the device on, standby, and completely off when held down and confirmed on screen). Next to the 'ON'-button will be a fingerprint sensor, as an alternative to numerical log-in on the touchscreen, to identify the operator of the device in an effort to safeguard the privacy of test results.

6.4. Conclusion

The user test was conducted with great satisfaction. Navigating the GUI was trivial, and consistently without error. Some affordances should however be strengthened, such as the vertical alignment of the reagents on screen and in the physical slide. Furthermore, the three capacitive buttons should be replaced by a fingerprint reader and 'ON'-button (figure 42).

Figure 42. Revision of the capacitive buttons

Chapter 7

Design finalization and showcase

7.1. Final design review

The design was finalized based on inputs from the user tests, and input from the project supervisors in a final design review. Figure 43 shows the final concept design that was taken into design review.

The device features a black glass front panel, with reagent slide, touchscreen display, and a capacitive button for power/standby. The reagents extend via a motorised hinge, where the operator can exchange the reservoirs. The device features a large, easy-to-read display.

The back of the device features a perimeter air vent for air intake. The recess at the bottom of the device hosts the outtake vent. Also on the back is the IO panel, which has room for power, ethernet, and USB connections, to connect to the medical practice intranet or to carry out remote software updates and to connect to a printer, respectively.

The device can be carried by holding the integrated carrying handle and by placing the other hand in the recess on the bottom of the device. This results in a comfortable carrying position as shown by figure 38 in the previous chapter.

Figure 43. Concept design for design review

This version was presented to the supervisors from Benchmark in a final design review. Based on the design review, some minor changes were made to the design of the device (also see figure 44):

Figure 44. Changes made in final design review

- While the old carrying handle was usable in an ergonomic fashion, this was not immediately apparent when looking at the device. To aid this, and in the process add an ergonomic one-hand way of carrying, a recess was added on the top of the device to serve as a handle. With this addition, the operator can carry the device with one hand.
- Next to this, the carrying handle was recessed from the body of the device, to create a more interesting detail.
- The sharp corner on the display was rounded off
- The amount of reagent storage was too small, so it was changed to ten reservoirs instead of five.
- For laboratory applications this amount will likely still be too few. To present an alternative, extra module add-ons for the device were thought of, for instance to house an additional large number of reagents.

*These extra module add-ons will be documented and iterated upon in chapter 8.4.

7.2. Final design

Thus, the design was finalized based on the final design review. Figure 45- 47 present renders and marketing materials showing the device and its characteristics.

The operator can interact with the device through the front UI panel. Alongside a fingerprint reader and capacitive power button, there is a large touchscreen to input commands. The reagents slide is below the screen, in vertical alignment. This makes it easy to read on the screen which reagents to exchange when refilling. The reagent slide and cartridge slot only open when the device is in the appropriate modus. This way, the operator will always be able to read on the screen what is happening and what steps should be taken next.

To perform a test, the operator turns on the device and should enter the testing screen via the GUI. The cartridge slot opens automatically, and instructions to take a cartridge, administer sample, and input sample identifier are shown on-screen. Thus, the operator administers the sample to the test-cartridge of choice and slides the cartridge into the slot. The device then recognizes the type of cartridge and associated test. After one last prompt testing commences and the device shows its progress.

When necessary, before entering the testing screen, the device may indicate a warning concerning reagent storage levels. This is when the operator may enter the reagent screen to refill or exchange reservoirs.

When a test is finished, the device will enter its automated cleaning cycle, and process the results. After calibrated error detection, the results are shown on screen and may be exported to a secure server/patient database, or to a printer. The device will be ready for the next test within one minute.

Figure 45. Final design and characteristics of the device

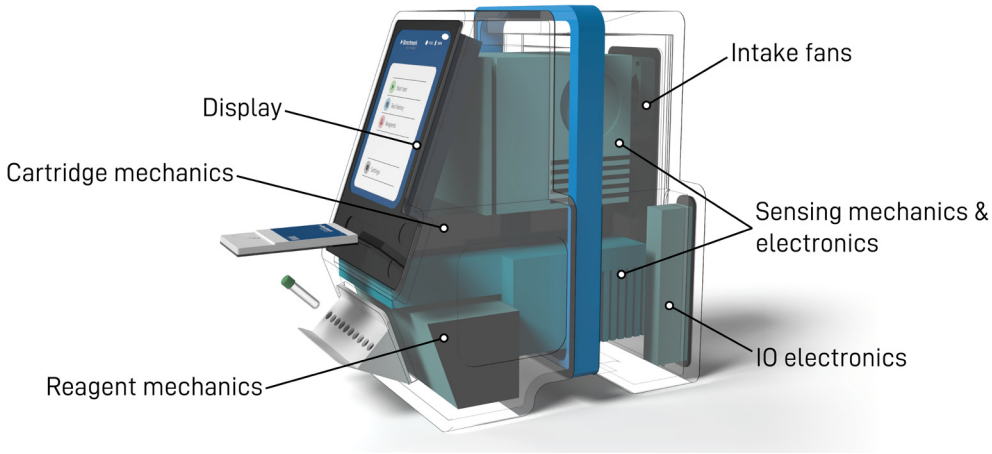


Figure 46. Final design internals of the device

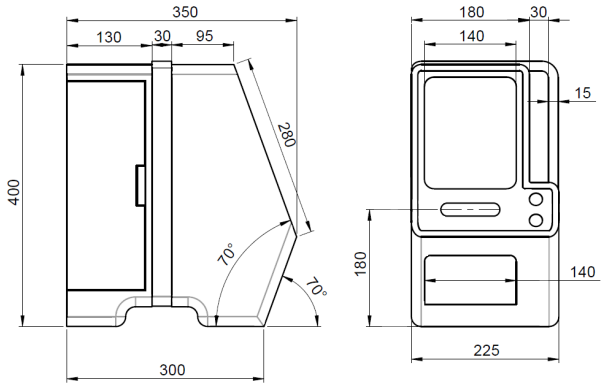


Figure 47. Side and front view with (some) angles and dimensions

7.2.1. Additions for laboratory variant

The laboratory version of the device will offer several features additional to the base/POC-variant: is the operator door (figure 48), through which the operator may expose the inner mechanism and exchange light filters within the optical measurement mechanics when necessary. Next, is the extra reagents interface on the right side of the device. In the future, a modular add-on for extra reagent storage may be connected to the main device from here (see chapter 8.4.3 for more on this). The laboratory variant will also be capable of more sensing methods, for better data collection and analysis. For instance, the optics stage may include a microscopic high-speed camera, to record the behaviour of droplets in the chip microchannels. Lastly, because of the extra complexities of the laboratory variant, it will need a wholly more sophisticated UI and more options for data export.

1. Operator door
2. Reagent add-on interface
3. More sensing methods
4. More sophisticated UI
5. More options for data export

7.3. Value proposition

The Benchmark device differentiates from what is currently on the market in two ways: 1) hosting the reagents not on the cartridge but in the device makes cartridges cheaper and easier to develop and manufacture, and 2) making the chip-to-world connections in the device means the device is compatible with a larger variety of microfluidic chips.

Consequently, independent pharmaceutical companies can develop microfluidic chips to be used in the cartridges with far lower associated costs, since reagent do not need to be freeze-dried or prepared for storage on a cartridge. Instead, chip manufacturers need to develop the chips with the ISO standard and the Benchmark chip-to-world connections in mind. Lastly, chips and cartridges could be reused after cleaning only, as there is no need to restock on-cartridge reagents.

Next, for doctors and practitioners what is appealing is that new test-cartridges can continually be developed around the same device. Since the chip-to-world connections in the device can be reused and combined into many possible combinations, this opens the door to an ever-expanding test palette. In the end, this saves the user from the need to invest in a new analysis device for every new test.

In short, its three benefits are:

- Reusable test cartridges and microfluidic chips
- Low microfluidic chip developments costs
- Continuous growth of test palette for the same device

The next pages show the updated platform sell-sheet.

Benchmark

Microfluidic platform

Since 1979, Benchmark has established a legacy of being a best-in-class solution provider and system integrator. By providing technology solutions, we are able to improve our customers' time to market, reduce risk and improve functionality by using our building blocks, platform technology and enhanced capabilities.

Among other solutions, Benchmark combines expertise from both engineering and advanced manufacturing to provide a state-of-the-art microfluidic diagnostics platform.

Benchmarks microfluidics platform is capable of accepting a variety of chips. Its micro-to-macro interface facilitates fluidic, pneumatic, and electric connections. In addition, the platform is capable of accepting a variety of chip sizes, thicknesses, and configurations, through its cartridge system.

Reagents stored in device

Micro-macro interface

Advanced medical diagnostics

Medical diagnosis

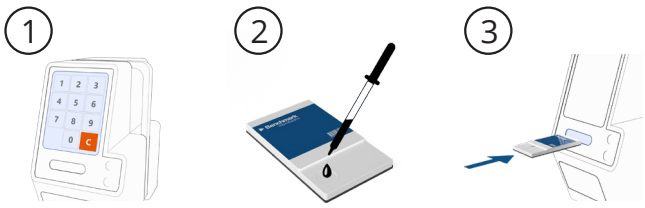
Storing reagents in the platform makes it cheap for researchers and pharmacuitical companies to develop microfluidic chips for medical assay purposes. Chip-to-world connections are facilitated by the platform, removing the need to carefully prepare and store reagents on-chip.

Benchmark's platform is capable of state-of-the-art sensing methods, which allow for a large variety of medical assays to be performed with the device.

The future of point-of-care diagnostics

Specifically developed microfluidic chip-based test cartridges offer quick diagnostics in POC settings, such as the doctors' office, ICU, and operating room. Benchmark's microfluidic paltform brings molecular diagnostics and immunodiagnostics into the POC environment, allowing for quick diagnostics at the bedside or in the doctor's office from only a very small untreated sample.

Since micro-to-macro connections are done in the device, the platform is capable of accepting an ever growing microfluidic chip-based test palette. This means the device does not need to be replaced when new test cartridges are introduced to the market.



Easy to use

Carrying out a medical assay with the microfluidic platform is simple, fast, and with minimal chance of error. Descriptive on-screen prompts ensure anyone can operate the device with only minimal training.

Benchmark Electronics
Lelyweg 10 | 7602 EA | Almelo, The Netherlands
+31 (0) 546 535 111 | www.bench.com

Benchmark

Chapter 8

Conclusion, recommendations, and future design directons

8.1. Introduction

While the core of the concept for the platform stands as the device is worked out and presentable, however, some directions are interesting to explore further. In the form of recommendations, this chapter highlights areas of the device which should be worked out more in depth. Next, future design directions are explored, such as possibilities for additions for a portable variant and modular addons.

8.2. Conclusion

This thesis concretises Benchmark's idea for a universal microfluidics-based platform for medical analysis and diagnosis. The initial design brief only very vaguely described Benchmark's overarching idea. With the design brief, two weeks of research (SoTA), and Wander Vreemanns prior thesis work on the micro-to-macro interface in mind, it was possible to concretise the platform and its functionalities.

The system architecture shows what components make up the device, and how they contribute to the common goal: fast, accurate measurements of on-chip behaviour. The major subsystems are pneumatics, sensing, electronics, and man-machine interfaces. While most of these were regarded as 'black boxes', the underlying functionalities and interplays were described.

The design of the device was done in an iterative process, with regular feedback from supervisors both from Benchmark and the University of Twente. In the end, the presented design feels mature and suitable in its use-case. While the design of the device was especially optimised for the POC market, small additions make it suitable for laboratory and research applications, as outlined in the previous chapter.

It is difficult to grade the final design to the requirements specification from chapter 5.5 since many of the functional aspects of the platform fall beyond the scope of this project. Nevertheless, it is safe to say the device adheres properly to the State Transitions and Man-machine Interfaces requirements, with only some minor exceptions (F15, NF2). Furthermore, most of the guidelines in chapter 5.6 were met, with the sole exceptions being guideline 7 and 9.

Weighing the final design against the guidelines stated in chapter 4.6 is more interesting. While aesthetical qualities are often subjective, it is safe to state the

device conveys robustness, reliability, and fits well in a medical environment. It is also reasonably suited to be cleaned or sterilised; however, the recess for the top handle is a compromise in this regard. Next, despite the GUI presented in this thesis being very preliminary, it does properly demonstrate a design direction that is self-explanatory resulting in easy operator. Another guideline the design adheres to is that the testing procedure should involve minimal operator steps: this was continually kept in mind during the design process; however, some compromises were made as to guide usability and reduce error.

On the other hand, some guidelines are still nearly impossible to comment on: consider guidelines 6 (the design of the Device should allow for repairs of the internal mechanism) and 8 (the amount of moving parts in the construction of the Device should be minimised). The current design is simply not detailed enough to comment on these. Thus, these requirements should be kept in mind and re-evaluated in the further development of the device.

The design process also raised a lot of questions that could not be answered within this thesis, simply because of time constraints, or because of the limited scope. Several interesting design ideas for the platform and its peripherals came up during the iterative process. These questions and design-directions will be briefly looked at in the following sections.

8.3. Recommendations

The largest problem with the current standing of development, is that almost none of the inner components and mechanisms of the device are defined. The scope of this thesis was very clear: to define the design language of the device and the interactions with the user. While part of this also included concretising the design problem and the device in the form of system diagrams and a requirement specification, these were not worked out further.

Therefore, the next steps in the development of the platform would be to start working on each separate subsystem and component. Only when each is sufficiently defined can be tested whether the design presented in this thesis holds. Furthermore, only when core functionalities are present can comprehensive UI/UX-design be done, and subsequent usability testing.

Nevertheless, this thesis does present a clear description, both textually and visually, of what should be the minimum viable product: how it looks and what it does. Interesting to continue working on though, are future design directions.

Such a modular and multi-functional device as this microfluidics platform has ample possibilities for further iterations and expansions.

8.4. Future design directions

8.4.1. Colour differentiation

Right now, the only difference on the outside of the device between the POC and laboratory-variants is the presence of the operator door. It may be worth considering implementing a second way to differentiate between the two versions of the device. When the difference between the versions immediately clear, there will be benefits for instance in customer support, or maintenance. For this, what may be considered is changing the colour accent based on the variant. The laboratory-variant may have the blue handlebar, while the POC-variant could be green (figure 49).

Figure 49. Render showing colour variation

8.4.2. Portable variant

Benchmark has repeatedly stated the wish for portability of the device to be taken into account during the design process. While the final concept accomplishes this, it is not suitable for rough environments. It would be interesting to define an additional functional variant, next to POC and Laboratory, for rough and demanding portable environments.

Ideally, this would be a subvariant of the POC-variant, specifically optimised for robustness and portability. It may be developed for use in field-hospitals, for relief efforts, or by military. Ideally, the portable device should have the same specifications as the regular POC-variant, but packaged in a rugged, carriable package. Desirable would be to also store an inventory of test cartridges in the same package.

To achieve this without designing a whole new device, a range of accessories could be introduced. These may include padding blocks and a display protector. Figure 50 shows some sketches showing ideas. Applying these accessories should allow for the device to be used in more demanding situations, like field hospitals, in a helicopter or ambulance.

Figure 51 shows a possible version of a rugged version of the device. Rubberized shock-dampening pads could be attached to critical corners of the device, to protect the plastic casing from damage. A screen protector should also be included. It should hinge to the top of the device when opened and kept shut magnetically. For this, magnets should be included under the glass display panel.

On the other hand, if the technology allows, Benchmark might opt for a suit-case form-factor. While in this case the device would not resemble the POC or Laboratory-variants, it could then be specifically designed as a complete ultra-rugged package.

Figure 50. Sketches showing initial ideas for device padding on critical corners

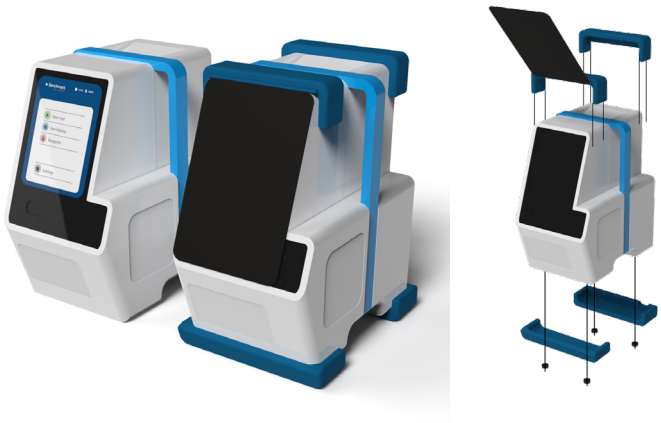


Figure 51. Renders showing possibilities for device padding and screen protector

8.4.3. Modular add-ons

During the final design review, the idea came up to expand the device family with additional modular add-ons. This may then extend the functionality of the laboratory variant of the device. For this, the main device should have interfaces on its side, to attach the addons. The two ideas that immediately came up were for 1) extra reagent storage, and 2) for accepting multiple cartridges at one time.

1) Extra reagent storage

Because of tough requirements for the laboratory-variant, there is a good chance a larger array of reagent storage will be needed. While the need for this should be investigated, it would be interesting to design a modular expansion that can be coupled to the main device. Figure 52 presents a design idea for this.

Figure 52. Possible design direction for a reagent storage module

2) Extra cartridge receivers

Another option is a module with additional cartridge receivers, to insert multiple cartridges for testing at one time. This would allow the operator to carry out tests where the sample travels through multiple test-cartridges before arriving in the sensing column of the main device, e.g. for measuring sample flow through multiple organs-on-a-chip.

Acknowledgements

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Complete list of LOC devices
Usability testing procedure

Appendix

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1. Complete list of companies and LOC devices

(adapted from the RIVM [5] with permission)

Company	Country	Name of device/chip/ system	M/D*	Application
Abaxis Inc	USA	Piccolo®	M	blood analysis
Abbott Diabetes Care Inc	USA	Xpress 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,
Abbott Point of Care Inc	USA	i-STAT® 1 Wireless	M	electrolyte analyses, lactate, coagulation, haematology 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

Company	Country	Name of device/chip/ system	M/D*	Application
Alere Inc	USA	Alere Triage® MeterPro	M	BNP, CK-MB, D-dimer, myoglobin, NGAL, troponin I, PLGF
Alere Inc	USA	Alere™ INRatio® / INRatio® 2PT / 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 ∑	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD ∑-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+® SELFCHECK	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
Beurer GmbH	Germany	GL 32	M	blood glucose

Company	Country	Name of device/chip/ system	M/D*	Application
Beurer GmbH	Germany	GL 40	M	blood glucose
Beurer GmbH	Germany	GL 44	M	blood glucose
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 (mulip-lex 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

Company	Country	Name of device/chip/ system	M/D*	Application
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,
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)

Company	Country	Name of device/chip/ system	M/D*	Application
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 D	infectious diseases, cardiovascular disease, cancer
LeukoDx Ltd	Israel	-	M	HIV / AIDS, sepsis, urinary tract infections
LifeScan Inc	USA	OneTouch® Ultra®2		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
Magna Diagnostics GmbH	Germany	MAZER™	D	technology based on magnetic nanoparticles
MBio Diagnostics	USA	MBio™ Diagnostics CD4 System	D	HIV diagnostics / CD4 count
MBio Diagnostics	USA	MBio™ Array System	D	multiple immunoassays; infectious diseases applications
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

Company	Country	Name of device/chip/ system	M/D*	Application
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
Philips Healthcare Radiometer Medical	Netherlands Denmark	Minicare AQT90 FLEX	D M	cardiac damage cardiac biomarkers
Radiometer Medical	Denmark	ABL90 FLEX	M	blood gases
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
Randox Laboratories Ltd	UK	Evidence Investigator	M	cardiac/cerebral biomarker (troponin I/brain-derived neurotrophic factor, glial fibrillary acidic protein, interleukin-6)
Randox Laboratories Ltd	UK	Vivalytic	M	Bacterial, viral respiratory tract infection array markers, STI array markers
Response Biomedical Corporation	Canada	RAMP	M	cardiac biomarkers (troponin I, NT- proBNP)

Company	Country	Name of device/chip/ system	M/D*	Application
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		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
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

Company	Country	Name of device/chip/ system	M/D*	Application
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
TearLab Corporation	USA	TearLab™ Osmolarity System	M	dry eye disease, ocular allergy
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),
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

*M/D: on the market / under development

2. User testing setup and procedure

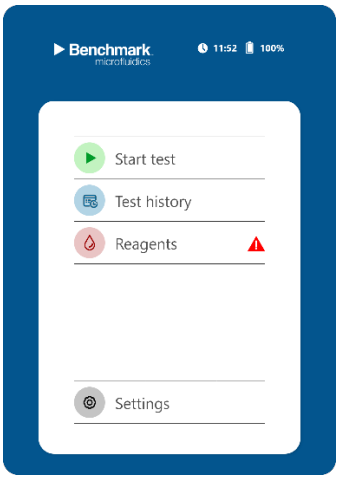
In the user test, participants were tasked exactly the following:

"Conduct a test using the provided cartridge"

During the test, their progress is monitored. Moments of hesitation with the UI and errors are recorded. After the test, each participant is given the opportunity to discuss their remarks.

The test setup is as follows: a lo-fi model of the device was placed next to a computer screen, on which the user could interact with the GUI mock-up. The model allows for exchanging reagent reservoirs and inserting/extracting the cartridge.

For the test, the GUI starts on the home screen showing insufficient reagents. Thus, the participant cannot immediately start a test, since the device gives a reagent warning. The participant thus needs to enter the reagent screen and exchange the reservoir to proceed with the test.



GUI starting screen

Photograph showing test setup