BACTERIAL PATHOGEN IDENTIFICATION IN BLOOD SAMPLES WITH ELECTRONIC NOSE TECHNOLOGY IN A CLINICAL SETTING

An early medical technology assessment of the µDtect

Master thesis Industrial Engineering and management – Healthcare technology & management

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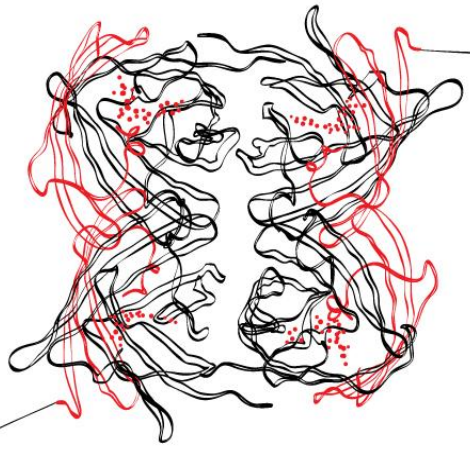

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Summary

Introduction: The use of antibiotics can cause undesired side effects for patient and on the micro-flora. Most infections are initially treated with a broad spectrum antibiotic until the causative agents and their susceptibility profile is known. Shortening the time to identification of the microorganism makes it possible to specify the treatment at an earlier point in time and reduce the risk of undesired side-effects. A new microorganism identification device is in development which has the potential to shorten the time to identification. The device makes use of an electronic nose which can detect volatile compounds. At the early stage of development it is uncertain where in the clinical setting the device should be placed and which direction of development should be aimed at in order to have the highest expected clinical and commercial value. An early medical technology assessment (MTA) is a 'toolbox' designed to support in product development decisions.

Methods: Within the framework of early MTA, a clinical case analysis, stakeholder analysis, early economic evaluation, and forces of entry analysis has been carried out. The clinical case analysis was carried out to identify the potential markets and the important bacterial pathogens. The stakeholder analysis was carried out to determine the professionals involved in the purchase and adoption process. This was followed by an early economic evaluation by means of a multiple criteria decision analysis (MCDA). Decisive attributes to adopt a new microorganism identification device were identified and evaluated. The performance of the µDtect and the competitors on the attributes was assessed. The last part of the early MTA was a forces of entry analysis to identify which threats and opportunities are present for the µDtect. The results from the four analysis parts were synthesized

Results: The clinical case analysis indicate that the µDtect has the highest potential within a microbiology laboratory. The Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, and the Eschericha Coli, were identified as important pathogenic bacteria.

The microbiology physician, laboratory manager, head of the department, hospital management, were identified as key stakeholders in the adoption of technology.

The clinical performance is deemed most important (0,56) category of attributes, compared to the cost of ownership (0,20), and the impact on workflow (0,24). The most important attribute for a microbiology identification device is accuracy (0.274). The µDtect performs well within the category cost of ownership and impact on workflow. On the attribute accuracy the µDtect has a low performance compared to the alternatives. On time to identification is the µDtect scores average.

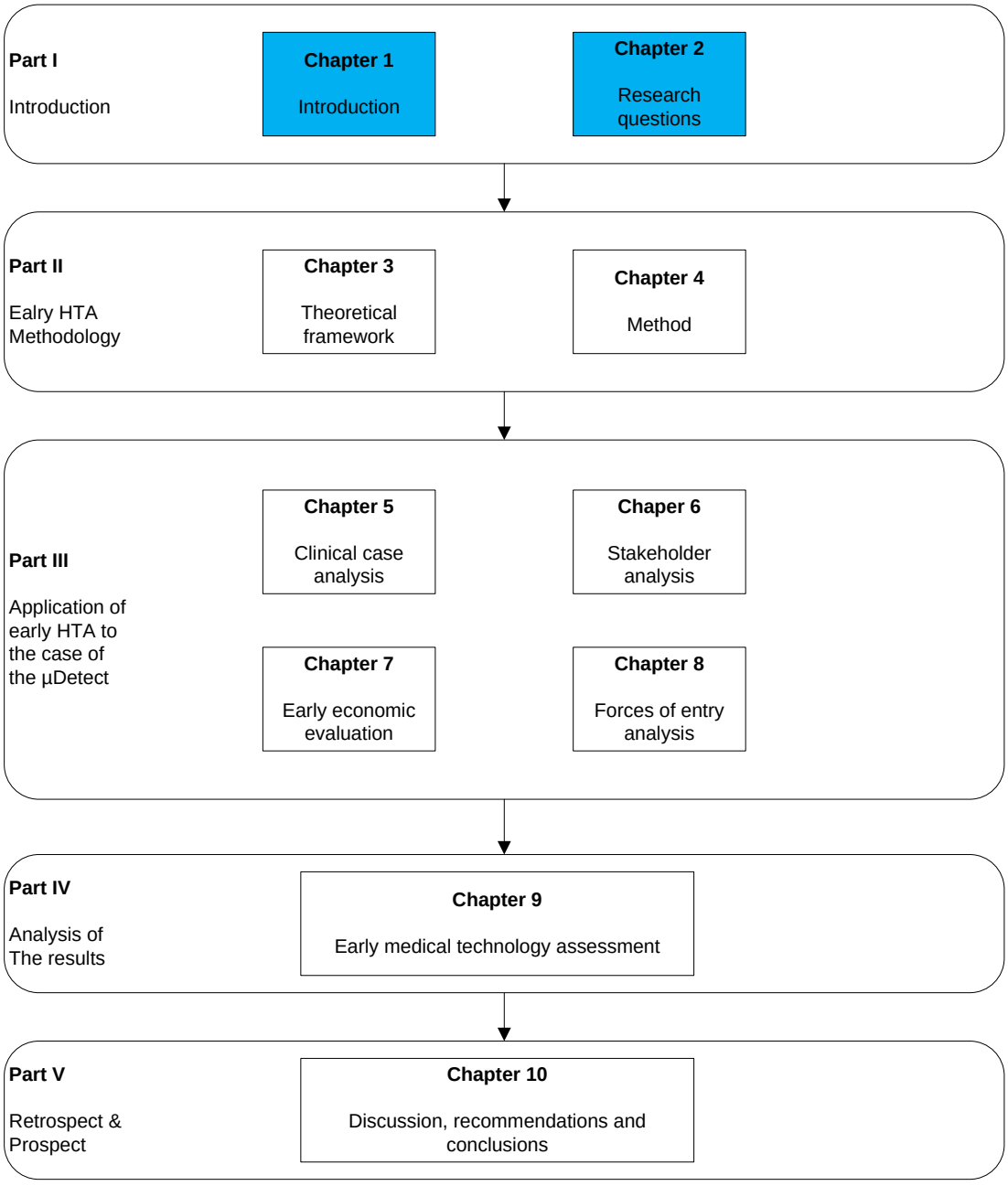
Certificates, proof of principle, and competitors are identified as critical forces of entry. The introduction process in a hospital and time to identification are identified as high priority forces.

Conclusion: The µDtect has potential in a clinical microbiology laboratory. Entering the Dutch market will be difficult for two main reasons; first, there is not much room for improvement due to the high standard set by the current state of the art. Second, the clinical market demands that a microbiology identification device can identify a broad range of microorganisms with high accuracy (95% or higher). Proof that the µDtect can perform accurate identification with patient materials has to be delivered. It is recommended that the development focuses on increasing the accuracy and delivering proof. The strategic choice of which pathogens to target for further development depends on the market the eNose company prefers to enter.

Contents

Part I

Introduction



1.0 Introduction

Infections are caused by pathogenic microorganisms. These infections can be treated with antibiotics which target these microorganisms. Most infections are initially treated with a broad spectrum antibiotic until the causative agents and their susceptibility profile is known, because there are a wide variety of microorganisms all with specific susceptibility profiles. As soon as results of determination and susceptibility tests become available, the antibiotic regimen can be selected[1]. The practice of selecting and drug targeting is important to optimize the efficiency of antimicrobial therapy, to reduce the development of drug resistance and other undesired side-effects on the microflora. Furthermore, possible toxic effects of broadspectrum antibiotic therapy, which sometimes include a combination of two different antimicrobial agents, can be reduced [2].

Shortening the time to identification of the microorganism is a way of streamlining the antibiotic treatment. When the microorganism is identified at an earlier point in time the antibiotic treatment can be adjusted. This leads to a more prudent use of antibiotics and may result in a better outcome for the patient. Hospitalized individuals, as well as individuals in the community, may benefit from the prudent use of antibiotics [3-4].

1.1 Microorganism identification

An early and specific identification of the infectious agents in blood can save lives and costs. In the Netherlands the process of identification is mainly done in medical microbiology laboratories. This process is still firmly based on traditional biochemical reactions. From the ages of Pasteur and Koch onwards, medical microbiologists have relied on classic culture-based methods in order to confirm bacterial infections and identify the pathogens involved [5].

In general, the process of identification of microorganisms is as follows: a sample, for example blood or urine, is taken from the patient and put directly into a culture bottle. These culture bottles contain a Ph indicator, and have a medium which provides an optimal environment for microorganisms' growth. The culture bottles are brought to the medical microbiology laboratory, which let the bottles incubate at 35°C for 8 to 12 hours. At this temperature and within this time, the microorganism present in the blood sample can grow. During this growth the microorganisms in the sample will metabolize, which induces a Ph shift. The indicator will change color due to this Ph shift, which will automatically be picked up by the incubator. At this time the bacteria is detected, but not yet identified.

A sample is taken from the positive flask and a Gram staining is conducted. The purpose of a Gram staining is to differentiate between Gram-positive and Gram-negative organisms, while simultaneously learning about the cellular morphology and arrangement. After a Gram staining, which takes less than a minute, a differentiation can be made between Gram-negative Cocci, Gram-negative rods, Gram positive cocci, and gram positive rods. This differentiation is important because each group is susceptible for different kinds of antibiotics. The information of the gram staining is communicated to the attending physician.

After the incubation the samples will be prepared to determine the susceptibility of the microorganism. This is done by culturing samples of the broth culture, by streaking upon Agar plates. An Agar plate is a Petri dish which contains a growth medium. Selective growth compounds are added to the media such as anti-growth compounds. The microorganisms are allowed to grow for at least four hours, but more often they are left overnight. The cultivation of the microorganism on the plates serves two goals: the first goal is to be able to tell something about the sensitivity and immunity of the microorganism, the second goal is to be able to isolate discrete colonies. The discrete colonies are used for the identification of the microorganism [6]. Several technologies are available which can rapidly identify the microorganism from the discrete colonies. The Matrix-assisted laser desorption/ionization time of flight mass spectrometer (MALDI/TOF-MS) is an example of a rapid identification technology which uses mass spectrometry to identify microorganisms. This identification can be done within several minutes, provided that sufficient bacteria have been collected prior to the mass spectral analysis [7]. Other examples of rapid identification techniques

are raman spectroscopy [2], Real time polymerase chain reaction (PCR) [8-9], and the 'lab on a chip' technology [9]. Not all of these techniques are already fully developed to be applied in medical microbiology laboratories, nonetheless they have potential.

1.2 µDtect

The eNose company has developed a technology that is able to identify certain bacterial species in blood samples during the incubation step of the process. The bacterium is identified at an earlier point in time compared to the current process and therefore makes it possible to select the correct antibiotics treatment at an earlier time. The device is called the µDtect (micro-detect) and makes use of the fact that bacteria produce volatile organic compounds (VOC's) and induce a pH shift when metabolizing in culture media. The VOC's will gather in the headspace of the culture flask. It has been demonstrated that a number of species can be both detected and identified by continuously analyzing the changes in headspace volatiles using an electronic nose device[10].

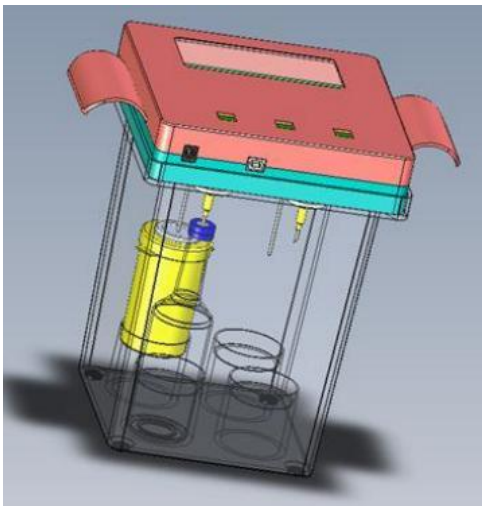


Figure 1: Schematic view of the µDtect

The µDtect uses an electronic nose technology to monitor the headspace of culture flasks over time using exposure-recovery mechanics. In the current practice the commercially available, pre-fabricated sterile culture flasks with integrated pH indicators are commonplace. The µDtect is designed to operate with these flasks. The flasks are fitted with a special designed disposable cap (Odocap®) which is placed on top of the culture flasks. The Odocap® has a round High Efficiency Particulate Air (HEPA) filter which allows VOC's to pass through to the sensor, but prevents microbes from passing. These VOC's are picked up by the electronic nose of the µDtect [10](see figure 1 for a schematic view of the µDtect).
The µDtect is extended with a colorimetric detection system. This detection system makes it possible to analyze the indicator at the bottom of standard culture flasks. This indicator changes of color under influence of the metabolism of micro organisms. By combining the information of the electronic nose and the colorimetric detection system firsthand identification is possible. Some bacteria, those with a strong 'smell', can be identified on the results of the electronic nose alone; others can be identified by combining the results of the smell and the indicator. The results will show a pattern over time, which will be compared with the known patterns in the database. The process of detection and identification by the µDtect takes about 8 to 12 hours. This is faster than the current practice and therefore the µDtect may be an added value for streamlining the identification process.
The µDtect also functions as an incubator and keeps the sample at about 35°C, which is the same as the current practice. This temperature is optimal for the growth of bacteria and therefore prepares the sample for further analysis. Early identification may lead to less follow up tests, which may result in a cost reduction.

1.2.1 Development of the µDtect

The first prototypes of the µDtect are developed, and still in an early development stage. There is a proof of principle that the µDtect can identify several bacteria effectively in blood samples [10-11]. The device has not been applied in a clinical setting yet and clinical trials with patient materials still have to be conducted. IJzerman & Steuten [11] describe a medical technology development framework which consists of four stages (Figure 2). During the path of development decisions need to be made, these decision problems differ for each stage. According to the medical product development framework, the development of the µDtect is in the translational research stage. Main decision problem for the industry in this stage is whether or not to invest in research and development and target the product to specific patient or customer groups.

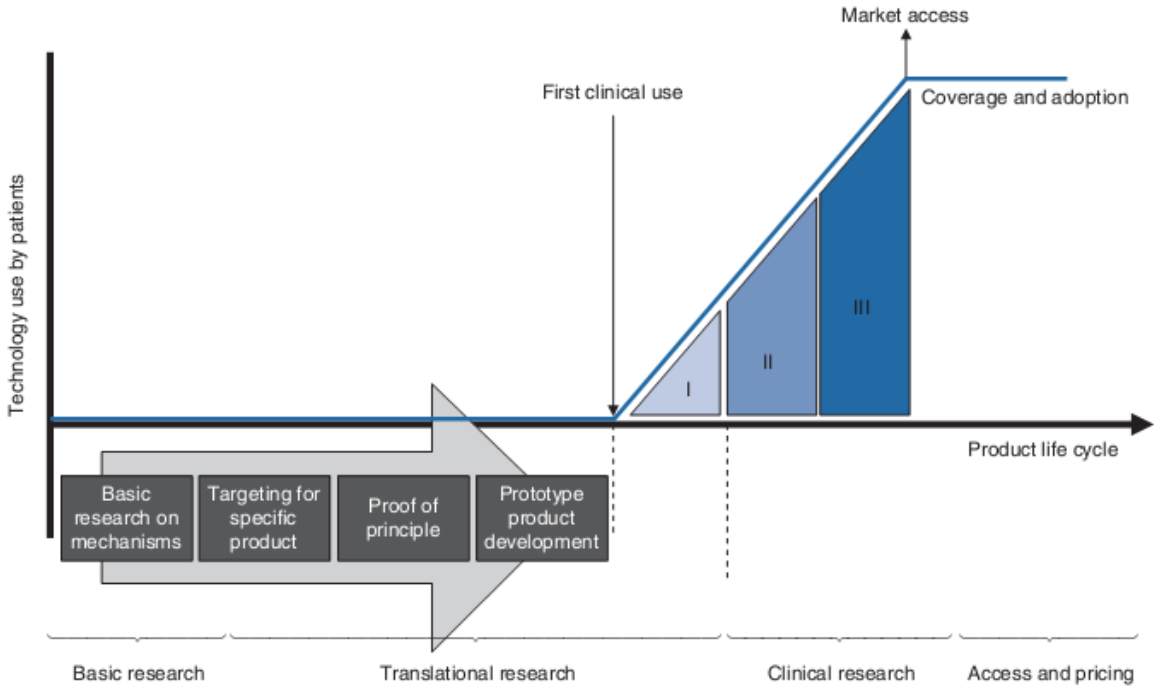


Figure 2: Product development stages (Adjusted from IJzerman & Steuten, 2011)

Information to support decisions concerning medical technology is usually gathered though a 'medical technology assessment' (MTA). An MTA is an objective assessment of the medical technology of safety, efficacy, and impact on patients as well as the effects of the technology on economic, judicial, and ethical aspects of the health care. Because the µDtect is still in development the assessment can be problematic. Performance and impact of a new technology is uncertain until it is used in practice. If a technology is put into practice already, it is a lot harder to make adjustments [12], and to influence the impact. It is important to be able to conduct a MTA in an early phase of development, whereas adjustments to the technology can still be made. Assessing the safety, efficacy, and the future (economic) impact in the early stages of development can be referred to as 'early medical technology assessment' (early MTA). Performing an early MTA can reduce uncertainties about major investment and design decisions [13]. Early MTA methods have been used in several studies and have shown that it can benefit the industry in a variety of ways. Research and development efficiency can be enhanced and potentially successful products can be identified at an early stage in the development [14].

The aim of this study is to assess in what setting the µDtect should be placed in the current clinical market and which direction of development should be aimed at in order to have the highest expected clinical and commercial value.

2.0 Research questions

The development of the µDtect is still in an early development stage. At the moment it is unclear where in the clinical health care setting the µDtect can add the most value. Furthermore, it is currently not known what the clinical needs and requirements for a microorganism identification device are, if one wants to introduce it to the market. These uncertainties can be addressed by conducting an early MTA. The main research question that will be addressed in this research is as follows:

In what setting in the clinical market should the µDtect be situated and which direction of development should be aimed at in order to attain the highest expected clinical and commercial value?

An early MTA does not consist of a predefined set of methods and tools. There are many tools and methods available to perform an early MTA. The selection of suitable methods dependents on the information required and on the stage of development of the product [11]. Currently, the development of the µDtect is in the translational research stage. For the construction of the early MTA, the following sub-question needs to be answered:

1. *Which methods and tools are suitable for performing an early MTA during the translational development phase and how will these fit into a model for assessing the µDtect?*

In order to provide direction for the development of the µDtect an assessment of the clinical potential is required. Potential settings where the µDtect can add value within the clinical health care market need to be identified. Information about the potential market and competitors and an indication of the importance of certain bacterial pathogens provides a context for the early MTA. The following sub-question addresses these aspects:

2. *Which are potential settings within the clinical health care market for an implementation of the µDtect and identification of which bacterial pathogens are of importance within these settings?*

To be able to introduce a medical device onto market it must comply with the clinical needs of the market. These clinical needs are set by the stakeholders as they determine whether a medical device will be acquired and/or used. Therefore the key stakeholders need to be identified. The following sub-question addresses this:

3. *Who are the key stakeholders when introducing or using a clinical microorganism identification technology?*

To be able to estimate the chances of entering a potential market, the performance of the µDtect must be compared with the performance of the (potential) competitors. The leading technology within the market, the current state of the art, sets the lower performance limit that is required for entering the market. The performance of the µDtect and the competitors can be compared based on attributes which are deemed important by the relevant stakeholders. The comparison provides information for development decisions for the µDtect. Answering the following sub-question will give insight in the performance and the required performance of the µDtect:

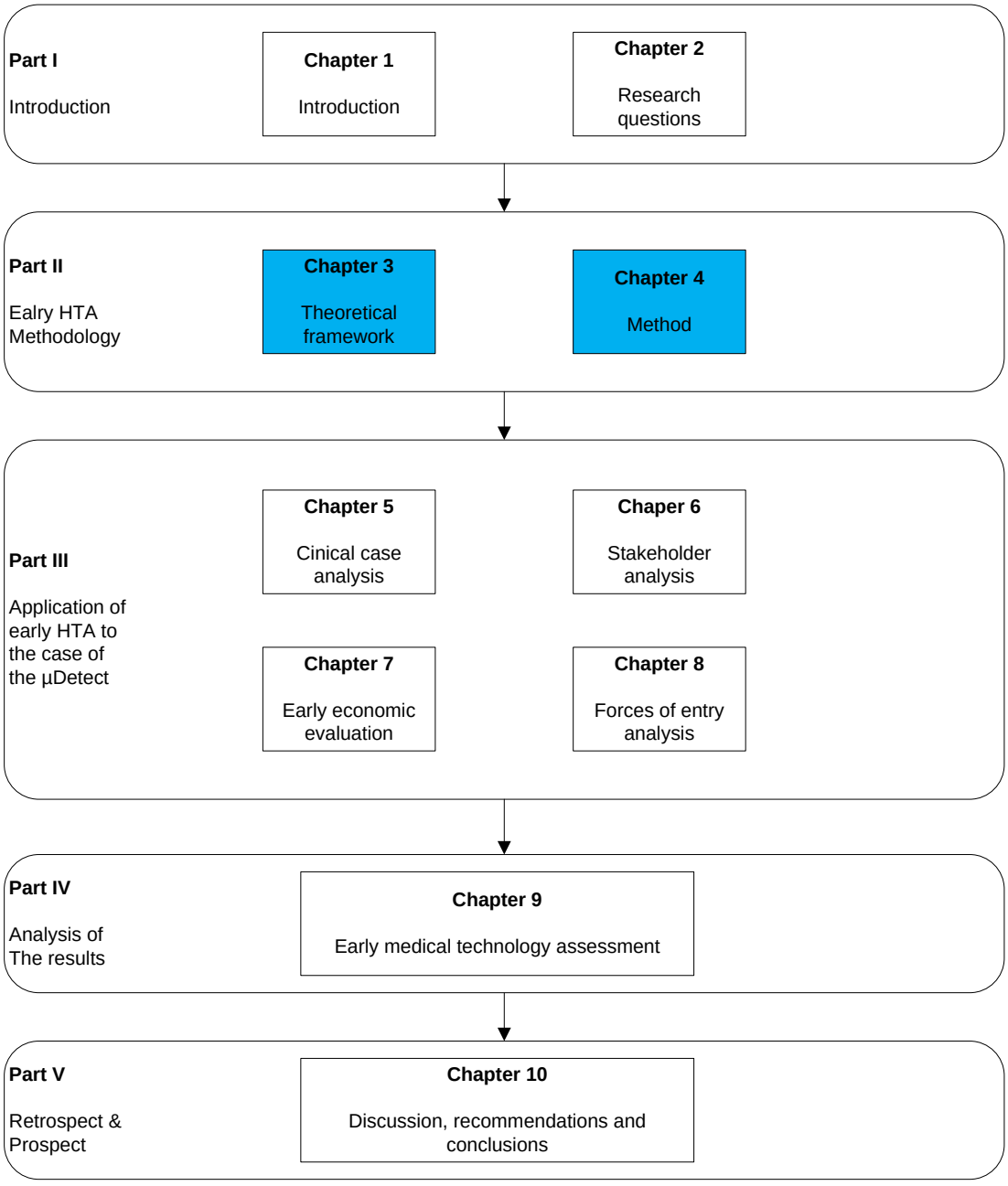
4. *What are the economic and performance attributes critical for introducing a microbiology identification device to the market and how well does the µDtect perform on these attributes compared to competing technologies?*

Forces of market entry influence an introduction of a new product. When these forces are ignored they can become barriers. If these forces are recognized they can be dealt with and possibly be turned into opportunities or strengths [15]. Therefore, it is important to identify the possible forces of entry and assess the way they will have influence on a possible introduction of the µDtect to the market. The potential barriers and opportunities can give an indication of the potential of the market and guide decision making about how to overcome the barriers or how to seize the opportunities. Therefore, the following sub-question needs to be answered:

5. *What are the forces of entry and how do these affect a possible introduction of the µDtect?*

Part II

Early health technology assessment methodology



3.0 Theoretical Framework

This chapter presents the theoretical base for the assessment model, which starts with a general description of the early MTA (3.1). This paragraph provides several tools and methods which are suitable for providing information to support development decisions in the translational research stage. The paragraphs thereafter will go into further detail of tools and methods, which are the clinical case analysis (3.2), stakeholder analysis (3.3), early economic evaluation (3.4) and the forces of entry analysis (3.5). In this chapter the advantages and disadvantages of each tool will be presented. Based on this theory a selection will be made of tools and methods which are suitable for this research.

3.1 Early medical technology assessment

Technology is generally defined as "science or knowledge applied to a definite purpose" [16] or as Galbraight [17]put it: "…the systematic application of scientific or other organised knowledge to practical tasks". Medical technology can be defined as "The drugs, devices, and medical and surgical procedures used in health care, and the organisational and supportive systems within which such care is provided" [18]. For example, a cardiac monitor is an example of medical technology. At the same time, an intensive care unit or one of its component parts being a monitor, is itself also a medical technology [19].

Technology assessment has been defined as a form of policy research that examines short- and long-term consequences of the application of technology. The goal of technology assessment is said to provide policy makers with information on policy alternatives [16].

3.1.1 Medical technology assessment

Since the 1970s, a MTA is used to support decisions of whether or not to implement new technologies into clinical practice [20-21]. MTA is a part of the much broader field of Evidence Based Medicine [22]. The rising costs of the health care sector were the incentive to look to the economic sector for solving the problems of the rising costs. This led to the development and application of cost-effectiveness analysis for the health care sector. It became apparent that besides the cost-effectiveness analysis much more information was needed to be able to assess technology in the medical field, resulting in the MTA [22]. Formally, a MTA is a broad assessment of the impact of a technology and is intended to include organizational, social, economic, and ethical considerations [23]. The aspects of assessing a medical technology are more than a cost-effectiveness analysis; social, legal and organizational aspects are of importance as well (Figure 3).

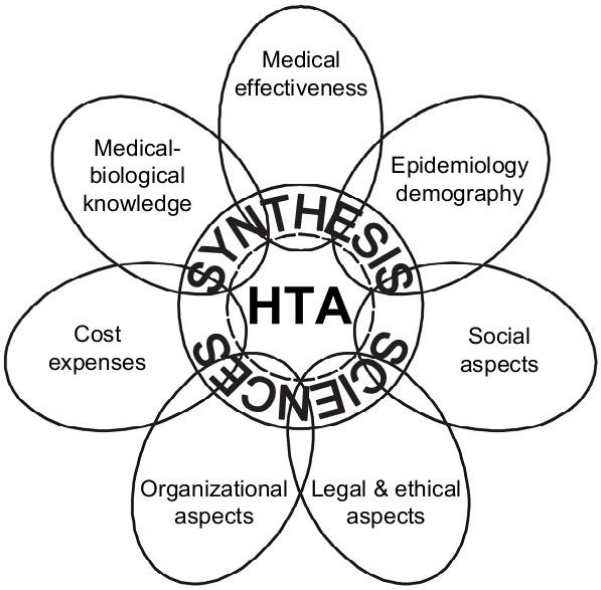


Figure 3: Aspects of a medical technology assessment (here referred to as a HTA)

A MTA is not a rigid pre-set of measurements, it can be adapted to the users own needs. Draborg et al. [24] conducted an empirical study in several countries about the use of MTA's. Four aspects were distinguished: clinical, economic, patient-related, and organizational aspects. It was shown that most MTA's focus on the clinical aspects and the costs. Leaving the patient-related and organizational aspects underexposed [13, 24].

The classical MTA has several shortcomings which makes it less useful for assessing medical technologies in the current market. Commonly, the focus is on the evaluation of a technology which is in the last stages of development or already on the market. With the timing of the classical MTA, the assessment is done after all the important investment and design decisions are made [13, 23]. Combining the late timing of the classical MTA and the fast changing world, the technology under assessment can already be obsolete or less useful in the changed environment. Performing the assessment at an earlier time point and assessing in an iterative way can deal with this problem. At the early stage lots of information will not yet be available. Integrating new information that comes available at the later stages of development should be taken into account in the assessment [13, 25-26].
A classical MTA is not a design for implementation. Douma [23] stresses that more attention should be given to aspects of technology dynamics by acknowledging the sociodynamic processes and in that way influence the technology's development and implementation in a desired direction.

3.1.2 Early medical technology assessment

As mentioned earlier the classical MTA has some shortcomings that make it less suitable for the current fast changing world. Conducting a MTA at an earlier time, the so called early MTA, in the lifecycle of a product can provide valuable information for development decisions. An early MTA tries to assess the (probable) safety, effectiveness and cost-effectiveness profiles of a new medical technology. It is performed in the earlier stages of the product development cycle as depicted in figure 4.

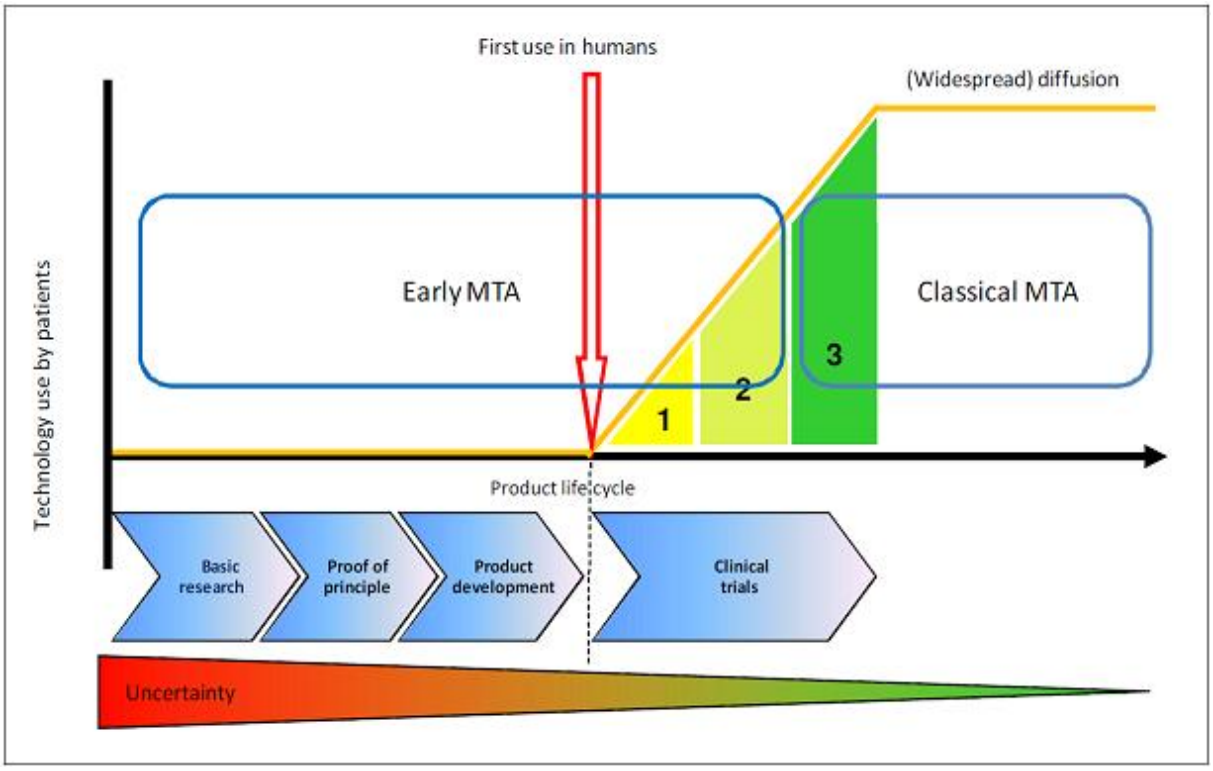


Figure 4: Early MTA during product development

IJzerman & Steuten [11] distinguish four different stages in medical product development, the basic research, translational research, clinical research and at last, the access and pricing stage. Roughly, the basic research stage focuses on the basic research on mechanisms. The translational research stage focuses on the targeting for a specific product, the proof of principle, and the prototype product development. In the clinical research phase the clinical trials will be performed. In the last stage the product will be brought on the market.

For each stage there are different tools available for conducting an early MTA, these are dependent on the goal of the stage. The assessment of probable safety, effectiveness and cost effectiveness are not the only relevant issues to inform decision making in the stages of development. Market size, patient needs, product specifications, implementation barriers and possible uptake, are issues that are relevant as well. Different stakeholders and considerations play a role in product development decisions, starting at the strategic level, followed by the business case, the clinical case and the financial proposition including the market access[11]. IJzerman & Steuten made an overview of useful tools for an early MTA which is depicted in figure 5. This research focused on the tools useful for the biomedical industry in the translational research stage. The strategic business case, multiple criteria analysis (MCDA), and the real options analysis were marked as very useful methods during the translational research stage. Health impact assessment and early health economic modeling were marked as useful.
Although these methods are likely to be used for a particular stage of research, there is considerable overlap and the choice of methods is dependent on the information requirement [11]. The information requirement for this research is in what form and in what setting the µDtect should be placed within the clinical setting. Therefore, potential markets need to be identified with the clinical needs and potential opportunities. The expected performance of the µDtect on the clinical needs gives an indication of the clinical and commercial value. The selection of tools is based on this information need.

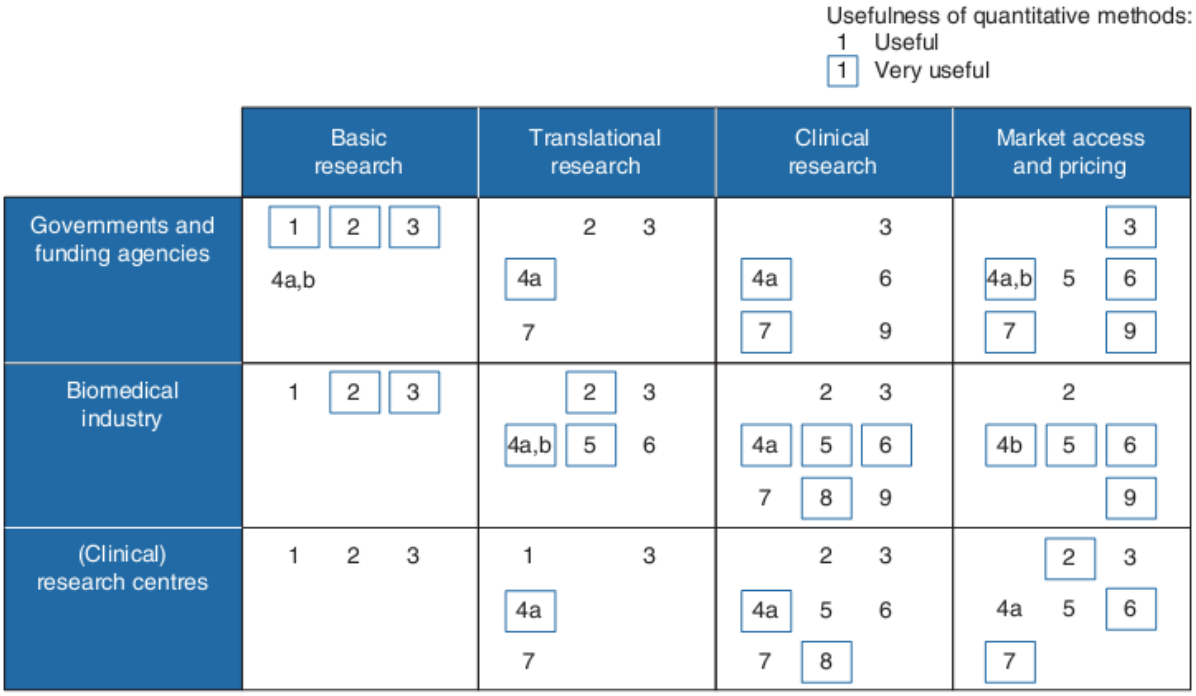


Figure 5: Quantitative methods used in early MTA. 1: Payback from research analysis; 2: strategic business case; 3: health impact analysis; 4a: MCDA; 4b: choice based preference methods; 5: real options analysis; 6: early health econonomic modelling; 7: horizon scanning systems; 8: clinical trial simulation; 9: value of information analysis [11]

3.1.3 Early Health Technology Assessment for the µDtect

In translational research the first decision to be made is whether the product or idea has clinical potential [27]. A clinical case analysis does structure the product features and potentials [11].

For the identification of the clinical needs it is valuable to know "who or what really counts". This principle, as described by Freeman [28], is the foundation of the stakeholder approach. For a possible introduction of the µDtect it is important to know who really counts in order to identify what is deemed important and to know who to approach.

An economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences [29]. Economic evaluation can be beneficially used in early phases of product development for a variety of purposes including early market assessment and research and development (R&D) portfolio management [14]. Within the economic evaluation multiple competing attributes are taken into account; MCDA methods are powerful tools to support decisions in case of multiple competing attributes[11].

To give an indication of the market access the identification of the forces that influence a possible introduction is required. These forces of entry can become barriers as well as market opportunities [15] and therefore are relevant to investigate.

3.2 Clinical case analysis

In translational research, the first decision to be made is whether the product or idea has clinical potential [27]. Following a clinical needs assessment and validation, it may therefore be appealing to incorporate a formal clinical case analysis in their decision framework. The clinical case analysis assumes a detailed overview of the clinical state of the art including existing products and their main advantages/disadvantages. A detailed overview of the market potential and the expected adoption of new products by opinion leaders and clinical experts should be present. A clinical case analysis does structure the product features and product potential, but does not yet quantify the decision alternatives nor does it include decision uncertainty [11].

When performing a clinical case analysis, the following questions are answered:

- What is the intended application/product?
- What are the new product's advantages?
- What is the target group?
- What are the comparator interventions?
- What is the expected clinical outcome?

Answering these questions will give an indication of the possibilities and the opportunities of the medical technology. Based on the answers of these question further investigation can be done with respect to health economic considerations.

3.3 Stakeholder analysis

To be able to deal with the changing and demanding environment of an organization or institutions it is valuable to know "who or what really counts". This principle, as described by Freeman [28], is the foundation of the stakeholder approach.
This principle consists of two parts: the "who or what" part and the "really counts" part. The "who or what" is the issue of stakeholder identification. How this is done will be described in paragraph 3.2.1. To determine the "really counts" part the importance of the stakeholder need to be determined. Mitchell [30] calls this: the salience. The definition of salience as stated by Mitchell is: "The degree to which managers give priority to competing stakeholder claims". This implicates that not every stakeholder are deemed as important, this will be discussed in paragraph 3.2.2.

3.3.1 Stakeholder identification

In the broad sense of the definition; stakeholders can be any group or individual who can affect or is affected by the achievement of the organization's objectives [28]. Mitchell et al. suggest that there are three attributes that makes it able to identify stakeholders. These attributes are power, legitimacy and urgency. If one or more of these attributes possessed by the individual or group, it can be identified as a stakeholder [30].

Power

Power is defined as: a relationship among social actors in which one social actor, A, can get another social actor, B, to do something that B would not have otherwise done [31-33]. It is the ability of those who possess power to bring about the outcomes they desire [32, 34]. Power can be exercised in different ways, or have different sources. Etzioni [34]makes a distinction based on the type of resource used to exercise power: coercive, utilitarian and normative power. Coercive power is based on physical resources of force, violence, or restraint, for example; threatening someone with a gun. Utilitarian power is based on material or financial resources; an example is to pay someone to do something for you. Normative power is based on symbolic resources. Love, esteem or prestige can be forms of normative power.

Legitimacy

According to Suchman [35], legitimacy is "a generalized perception or assumption that the actions of an entity are desirable, proper, or appropriate within some socially constructed system of norms, values, beliefs, and definitions". This defini tion implies that legitimacy is a desirable social good, that it is something larger and more shared than a mere self-perception, and that it may be defined and negotiated differently at various levels of social organization [30].
The attributes of power and legitimacy can be combined in order to create authority [33].

Urgency

Urgency is the degree to which stakeholder claims call for immediate attention [30]. In other words, urgency exists when two conditions are met: (1) when a relationship or claim is of a time-sensitive nature and (2) when that relationship or claim is important or critical to the stakeholder (Mitchell et al, 1997).

Additional features of stakeholder attributes

A stakeholder is in the possession of one or more of the attributes described above. This makes it possible to make a classification of stakeholders and to be able to predict their salience. Before that, several important features of the attributes should be addressed. First, the stakeholder attributes are variable, not a steady state. This is important aspect because it implicates that the salience of the stakeholder can change, or be influenced. For example: power is transitory, when exercising utilitarian power by buying a product or service, there is a transition of financial assets and therefore power. Second, the attributes are socially constructed, not objective. The degree of an attribute being present is constructed from multiple perceptions. Third, a stakeholder may not be conscious of possessing a certain attribute or, if conscious of possessing the attribute, may choose not to act on it.

3.3.2 Stakeholder classification

Mitchell et al. developed a typology in order to be able to classify stakeholders. Based on combinations of the attributes described above they identified 8 classes. The model, the so called "stakeholder salience" is presented in figure 6. The salience of each stakeholder class differs. Mitchell et al. [30] argues that the more attributes there will be present, the higher the salience. In other words, stakeholders who can only claim one attribute have a low salience, stakeholders who can claim two attributes have moderate salience, and stakeholders who can claim all three attributes have the highest salience.

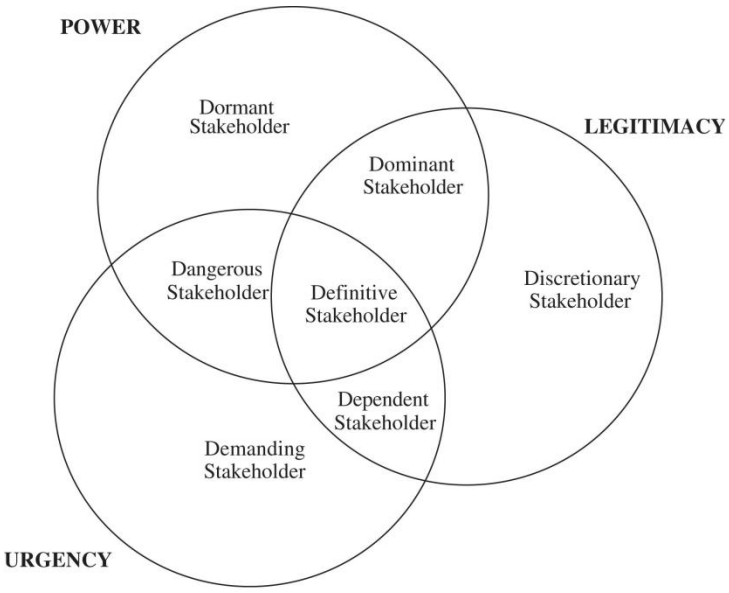


Figure 6: Salience model

An overview and explanation of the different stakeholder classes with their relevant attributes can be found in table 1.

Stakeholder	Attributes	Salience	Explanation
Dormant	Power	Low	Dormant stakeholders possess power to impose their will on a firm, but by not having a legitimate relationship or an urgent claim, their power remains unused. Normally they have little interaction with the firm, but the potential to acquire a second attribute. With either legitimacy or urgency they will become more salient to the firm.
Discretionary	Legitimacy	Low	Because of the absent of power and urgency there is absolutely no pressure on managers to engage in an active relationship with a discretionary stakeholder.
Demanding	Urgency	Low	Demanding stakeholders, those with urgent claims but

			having neither power nor legitimacy, can be bothersome but not warranting more than passing management attention.
Dominant	Power, Legitimacy	Moderate	Stakeholders who are both powerful and legitimate have their influence in the firm assured. Another term for when these two attributes are present is "authority".
Dependent	Legitimacy, Urgency	Moderate	Stakeholders who lack power but have the urgent legitimate claims are dependant, because they need the power from other stakeholders or the firm's managers to carry out their will.
Dangerous	Power, Urgency	Moderate	Stakeholders who have the urgency and power, but not the legitimacy, will probably be coercive and violent and therefore dangerous. Sabotaging a project can be such a coercive action.
Definitive	Power, Legitimacy, Urgency	High	When a dominant stakeholder's claim becomes urgent, and therefore becomes a definitive stakeholder, managers have a clear and immediate mandate to attend to and give priority to that stakeholder's claim.
Non-stakeholder	None	None	These people have no attributes and therefore no claim. Technically they are no stakeholders.

Table 1: Stakeholder classification

3.4 Early economic evaluation

A new technology, like the µDtect, cannot be brought upon the market when it is not know whether the market has need for the product. The clinical needs have to be identified, along with the critical promoting and demoting factors when adopting a new microorganism identification device. After this identification it is possible to compare the performance of the µDtect and its competitors on those success factors. This part of the analysis is called the early economic evaluation.

An economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences". The basic goals of an economic evaluation are to identify, measure, value and compare costs and consequences of the alternatives being considered [29]. Economic evaluation can be beneficially used in early phases of product development for a variety of purposes including early market assessment, R&D portfolio management and first estimations of pricing and reimbursement scenarios [14]. In the early stages of product development relative simple economic evaluations can provide a rapid indication of the potential cost and effectiveness of a product. In later stages of development, when more information becomes available and attention is centered on fewer products a more in depth analysis can be conducted [25]. Including the costs and effectiveness alone is a too narrow view when making an investment decision. Multiple criteria, qualitative as well as quantitative, play a role which makes the decisions complex. Methods like cost-effectiveness analysis, cost-benefit analysis, burden of disease analyses, and equity analysis, only concentrates on a single criteria. In reality, multiple criteria are taken into account by decision makers [36]. Multi-criteria decision analysis (MCDA) is a powerful tool to support decisions in case of multiple competing criteria [11]. The use of MCDA methods in an early economic evaluation will be further explored below.

3.4.1 Multiple criteria decision analysis methods

There are several MCDA methods available, for example simple multi-attribute rating technique (SMART), the Analytical Hierarchy Process (AHP) and conjoint analysis (CA). AHP and CA are two

methods which are used frequently for decision making in the health care setting [12, 37-39]. SMART can be an attractive option because of its relative simplicity and transparency [40-41]. Therefore, these three MCDA methods will be discussed in further detail below.

SMART

SMART has been widely applied as a MCDA method because of its relative simplicity and transparency. Therefore, decision-makers from many different backgrounds can easily apply this method and understand its recommendations. SMART will not always capture the detail and complexities of a decision, but it is an effective way for illuminating the important aspects of a problem and how they relate to each other [40].

The SMART method consists of eight stages:
Stage 1: identify the decision context
Stage 2: identify the alternatives
Stage 3: identify attributes that are relevant to the decision problem
Stage 4: Measure the performance of the alternative on that attribute
Stage 5: Determine a weight for each attribute
Stage 6: For each alternative, take a weighted average of the values assigned to that alternative
Stage 7: Make a provisional decision
Stage 8: Perform a sensitivity analysis.

Roughly, these steps can be found in any MCDA [41], differing between the usage of tools in stage 3 to 5 The possible tools for each stage will be discussed in detail in the paragraphs below (3.4.2 – 3.4.4).
SMART uses a value tree for identifying relevant attributes in stage 3, in which one branch represents the costs and the other branch the benefits. In stage 4, the measuring performance is done by 'direct rating'. The weight for each attribute is determined by the use of swing weights in stage 5 [40].

Analytical Hierarchy Process

The AHP is a technique developed by Saaty [42]and is widely used as a MCDA method in the health care setting [12, 37, 39]. AHP engages decision makers in breaking down complex decisions into smaller parts, which are ordered in a decision hierarchy. A decision hierarchy is similar to the value tree used in SMART, the main difference is that the alternative courses of action appear on the lowest level of the hierarchy.
For determining the relative importance of attributes, and to compare how the options perform on the different attributes, pair-wise comparisons throughout the hierarchy are made. These pair-wise comparisons are made by using a rating scale. This scale uses intensity 1 to 9 to represent relative importance (Table 2).

Intensity of relative importance	Definition	Explanation
1	Equal importance	Two activities contribute equally to the objective
3	Moderate importance	Experience and judgement slightly favour one over another
5	Essential of strong	Experience or judgement strongly favours one over another
7	Importance demonstrated	An activity is strongly favoured and its dominance is demonstrated in practice
9	Extreme (absolute)	The evidence favouring one activity over another is of the highest possible order
2,4,6,8	Intermediate values	When compromise is needed

Table 2: Scales used in AHP

Based on the pair-wise comparisons it is possible to calculate an inconsistency ratio, which gives an indication of the consistency of the decision-makers preferences.

The strength of the AHP is that pair-wise comparisons are easy to perform. It means that the decision-maker can focus on each small part of the problem. Furthermore, the consistency of the preferences can be checked.

Weakness of the AHP method is the conversion from the verbal to the numeric scale. It is argued that this conversion does not always reflect the preference of the decision-maker [43]. Another disadvantage is that when new alternatives are introduced they can reverse the ranking of existing alternatives. The AHP should be redone when this is the case. Another argument against the AHP is the number of pair-wise comparisons, which can become very large when there are many attributes and/or alternatives to evaluate [40].

Conjoint Analysis

The conjoint analysis method originates from the field of market research and has been successfully applied to the health care sector. The conjoint analysis starts with identifying the characteristics or attributes and levels are assigned to the characteristics. These levels can be cardinal, ordinal, or categorical. Based on the characteristics and the levels chosen, scenarios are drawn up. The number of scenarios increases with the number of characteristics and levels. Normally a choice is made by the researcher to limit the number of scenarios to a manageable level.

The preferences for scenarios are elicited from respondents, normally by means of a questionnaire. Figure 7 shows an example of a conjoint analysis question.

This preference elicitation can be done by means of ranking, rating, or discrete choices. Regression techniques are used to analyse the responses [39].

Figure 7: Example of a CA question

The strength of the CA method is the rigorous method of eliciting preferences when a few scenarios are available. This allows an estimation of the relative importance of different aspects of care and the trade-offs between these aspects. A weakness of the CA method is that it gives quickly raise to many possible scenarios when there are many characteristics under consideration. Furthermore, the CA method gives no detailed insight into the relative importance of the characteristics.

3.4.2 Identifying attributes

Identification of the relevant attributes is the third stage of an MCDA. Interviews or focus groups are suitable methods for gathering information about which attributes are of importance for a decision. A value tree or decision hierarchy can be constructed from the attributes. The tree starts with the goal on which the main attributes have influence. When a (main) attribute is unclear, or not measurable, it should be broken down into sub-attributes. Following this method, a tree is constructed with different levels which represent how different attributes affect the decision [40]. Keeney & Raiffa [44] have suggested five criteria that can be used to judge the value tree:

- *Completeness*: the tree is complete when all the attributes that are of concern to the decision-maker are included.
- *Operationality:* This criterion is met when all the lowest-level attributes in the decision tree are specific enough for the decision maker to evaluate and compare them for different options.
- *Decomposability:* The attractiveness of an option on one criterion can be assessed independently of its attractiveness on other criteria.
- *Absence of redundancy:* There are no duplicating attributes in the value tree.
- *Minimum size:* Attributes should not be decomposed beyond a level where they can be evaluated. In other words, the tree should not be too large which would make a meaningful analysis impossible.

3.4.3 Measuring performance

Measuring the performance of the alternatives on the attributes is stage four in a MCDA. The performance of the alternatives on the attributes can be shown in a performance matrix. In a performance matrix, each row describes an alternative and each column describes the performance of the options against each attribute. The performance measurements can be qualitative descriptions, natural units, or on a numerical scale.

The performance can be transformed to a numerical strength of preference scale. Better performing alternatives score higher on the scale, which can mean reversal of natural units. For example: lower

costs are perceived as better, so a lower cost price should get a higher score. In practice, scales extending from 0 to 100 are used, where 0 represents the worst performing option and 100 the best performing option on a certain criteria [41]. The transformation makes the attributes comparable and an overall utility of the alternatives can be calculated. The transformation of the performances is most commonly done by point estimates on an interval scale [45].

It is argued that point estimates have several disadvantages:
1: They do not address the fuzzyness of decision problems [33].
2. It is difficult to map qualitative preferences, which may have a range [46-47].
3. Decision makers often operate in situations where incomplete information makes it impossible to assign point estimates to decision alternatives [33, 47].

A way of dealing with these disadvantages is to work with intervals. By estimating a minimum and a maximum value on the interval scale, the minimum and maximum utility of each alternative can be estimated [33]. This will give an indication of how well each alternative could perform. If during development new information becomes available, the utility ranges will become more accurate.

Point estimates on an interval scale
Assigning a value score between 0 and 100 on an interval scale is a conventional method. The first step in establishing an interval scale for an attribute is to define the levels of performance corresponding to two reference points on the scale, which are usually the extreme scores of 0 and 100. This can be done by global or local scaling. Global scaling is assigning the score of 0 to the worst and 100 to the best level of performance that is likely to be encountered in the decision problem. Local scaling associates 0 with the performance level of the alternative in the currently considered set of alternatives which perform least well and 100 with that which performs best. An advantage of global scaling is that it more easily accommodates new alternatives at a later stage. Disadvantages of a global scale are the extra judgments needed in defining the extremes and that it is less convenient than local scaling for the construction of relative weights. When the end points are established for each attribute, there are three ways in which scores may be established: value function, direct rating, and comparison based rating.

Value function
The use of a value function can translate a measure of achievement on an attribute into a value score on the 0 – 100 scale. For practical purposes the value function is often assumed to be linear. However, on some occasions it may be desirable to use a non-linear function, because a linear function may not represent the reality [41].

Direct rating
Direct rating is used when a commonly agreed scale of measurement for the criterion in question does not exist, or if there is no time or no resources to undertake the measurement. Direct rating uses the judgment of an expert to associate a number in the 0 – 100 range to each attribute for each alternative. Consistency can be a problem with direct rating and the rating is very dependent on the expert in question, which makes it vulnerable to bias [41].

Comparison based rating

Another way of establishing a score is to make a series of verbal pair-wise assessments expressing a judgment of the performance of each option relative to each of the others. Several methods make use of this technique, like for example AHP is an example of such a method. An advantages is that consistency can be checked, a disadvantage is that is can cost a lot of time to make all the comparisons [41].

3.4.4 Assigning weights to attributes

A unit of performance assigned to one attribute does not necessarily equals a unit of performance on another attribute. Therefore weights need to be assigned to the attributes, which is stage five of a MCDA. Weights make comparison possible and allow for the calculation of the expected utility of each alternative. There are several techniques available to determine the weights. These techniques are mainly trade off or choice based techniques. A selection of these techniques is discussed below.

AHP makes use of pair-wise comparison between attributes. As pointed out above, strong points of this method are that it is easy to perform and the consistency can be checked. A weak point is that the number of comparisons that have to be made can become very large when there are many decision attributes to compare [40].

SMART makes use of swing weights to elicit weights for attributes. With this method, respondents are asked to compare a change from the least preferred to the most preferred value on one attribute with a similar change (swing weight) in another attribute. For respondents, this method can be not very intuitive to use. It can be hard to imagine a swing by the respondent and weight it against another attribute[40].

Allocation of points, or budget pie method, is a technique where a certain number of points are allocated over the decision criteria on the same level. The more points allocated to a criterion, the more important it is deemed. This method forces the decision maker to think about trade-offs and strength of preference between the criteria. Advantages of this method are that it is intuitive and fast to perform [48-49].

The willingness to pay method asks the respondent to express the importance of an attribute into monetary terms. This system is easy to understand for respondents, but the questions can be hard to answer. Expressing the value of health into monetary terms can be difficult and respondent may object to it [48].

Dealing with missing data

Several methods are available to deal with missing data: Case wise deletion method, and single or multiple imputation methods [50].

Case wise deletion method is that if any of the available variables has a missing value for a particular case, this case is omitted from the analysis, which may cause a huge waste of data.

Single or multiple imputation can be done by means of several techniques. Estimating and imputing a value can be done based on values of other cases in the same class. Using the means of these values is a way of dealing with the missing data, but is not recommendable when one is interested in the variance of the data. Scheffer [50] advises that this method should only be used when there is no less than 10% of the data missing and one is only interested in the mean.

3.4.4 Sensitivity analysis

Sensitivity analysis provides the means for examining the extent to which vagueness about the inputs or disagreements between people makes any difference to the final overall results. It is a way of exploring uncertainty in the results of economic evaluations. Sensitivity analysis examines the effect on the result of using different assumptions around the parameter estimates [51]. There are different types of sensitivity analysis:

- *Univariate analysis*, also called a one way simple sensitivity analysis. One parameter is varied to see how it affects the results.
- *Scenario analysis*, this is a multi way simple sensitivity analysis. Two or more parameters are varied at the same time and overall effects on the results are evaluated.
- *Threshold sensitivity analysis*, this examines the critical value of parameters above or below which conditions the results the study will change.
- *Probabilistic sensitivity analysis*, by which probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques. The Monte Carlo simulation is an example of such a technique[51].

3.4.5 Early economic evaluation applied to the µDtect case

The main goal of the early economic evaluation is to identify the critical success factors and make a comparison between the performance of the µDtect and the performance of the competitors on these factors. To attain this; the eight steps as described under SMART will be applied. Step 3 to 5 will be customized in order to fit this research and therefore a customized MCDA will be used.
Constructing a value tree, like in SMART and AHP, is valuable in this research because it gives a structured overview of the important aspects and how they relate to each other.

Comparison based measurement of the performance, like in AHP, can cost lot of time. If an attribute or alternative is added the comparisons have to be redone. For assessing alternatives which are in the (early) development stage this is not preferred, because changes are likely to occur. The performances on the attributes of the alternatives are not known for sure. The linear value function is easy to use and adjust when changes occur. This is less the case with direct rating which is based on the opinion of the expert. Change of the performance requires conducting the direct rating again. Therefore a linear value function is the best option for translating the performance of the alternatives into point estimates on an interval scale.

Identification of the critical success factors is important for the development of the µDtect. The measurement of the importance does not have to be exact in order to give an indication of the important factors. Therefore a quick and intuitive method to determine the preferences is suitable. Pair-wise comparison method can require a lot of time, the swing weight method and willingness to pay method can be hard to apply. The budget pie method is easy to use and quick to perform. Although the inconsistency can not be checked, it is suitable for the assessment in this research.
The sensitivity analysis allows to predict answers to “what if” questions. These questions are of interest for development decisions. Scenario analysis makes it possible to evaluate the effects of focusing on certain directions of development. This makes it a valuable tool for the early economic evaluation of a product in a development stage.

3.5 Forces of entry analysis

In 1979 Porter described how competitive forces shape strategy. He stated that awareness of these forces can help a company stake out a position in its industry that is less vulnerable to attack. One of these forces was the threat of entry. New entrants form a threat, although the seriousness of the threat depends on the introduction barriers [52]. For entrants these barriers can form a serious problem when they want to enter a market.

Herzlinger [15] analyzed the health care market in the United States. She noticed that a lot of money is invested in research of medical technology, a lot of discoveries are done and innovative technologies are developed, but the introductions of these innovations are often unsuccessful. She identified six forces that can drive innovation, but as easily kill it as well. These forces are described in the table below.

Players	The health care sector has many stakeholders, with their own agenda. Often, these players have substantial resources and the power to influence public policy and opinion by attacking or helping the innovator.
Funding	There are two kinds of financial challenges: funding of the innovation's development and figuring out who will pay how much for the product or service it yields.
Policy	Government regulation can aid or hold back an innovation. It is important for innovators to understand the extensive network of regulations that may affects a particular innovation and how, and by whom these rules are enacted, modified, and applied.
Technology	As medical technology evolves, understanding how and when to adopt or invest is critically important.
Customers	The empowered and engaged customers of health care are a force to be reckoned with in all types of health care innovation. A company should recognize the consumers' sense of empowerment and their actual power.
Accountability	Important stakeholders are demanding accountability to the innovators. They require that technology innovators show cost-effectiveness and long-term safety, in addition to fulfilling the shorter-term efficacy and safety requirements of regulatory agencies.

Table 3: Six forces of innovation by Herzlinger (2006)

Each of the forces described above can become a barrier of innovation when they are not acknowledged and managed [15, 53]. Therefore, identifying and analyzing these forces for a new medical technology can be of importance for the decisions made during the development process.

3.5.1 Forces of entry identification

There are several methodologies to identify possible forces of entry. The difference between the methodologies is based on the method of data collection. Cochrane et al. [53] distinguished three main groups: survey methods, interview methods, and focus group methods.

Survey methods

There are only a few surveys which comprehensively examine barriers based on an existing framework or model. One exception is the comprehensive barrier assessment; BARRIERS [54-55]. This method is based on the theory of diffusion of innovation. A questionnaire examines 29 factors grouped around 4 characteristics important to the adoption of change: the characteristics of the adopter, the organization, the innovation, and the characteristics of the communication.

Barrier questions are frequently stated like; “What are the challenges for implementation of the technology?” or, “What do you perceive are the limitations of the new technology?”. Categorical dichotomous (agree/disagree) or Likert-type scale response items relating to specific barriers are used as well. The survey method makes it possible to analyze frequencies, mean scores, and simple difference between groups.

Interview methods

Interview methods can have structured, semi-structured formats incorporating closed or open ended questions or both. Interviews tend to identify more organizational, system, and support barriers than the other methods. More specifically, questions that are open-ended serve a more exploratory function, revealing unanticipated barriers to targeted practices, while close-ended questions served to measure predefined barriers [53].

Focus group methods

Focus group methods are designed to explore specific topics in depth. Focus groups are especially useful for comparing emerging themes against a priori taxonomies and frameworks or for building new theories [53].

3.5.2 Forces of entry assessment

After the identification of the possible forces of entry an assessment should be made to determine the potential strength of the barrier/opportunities as an obstacle to innovation. Existing theories and models strengthen the design of the forces of entry assessment. Nonetheless, most researches in which forces of entry are assessed are poorly framed. Most studies do not look at any theoretical framework or conceptual model to guide the design and analysis and examine only one or a few barriers [53].

Cochrane et al. distinguished three types of methods for analyzing data on possible barriers/opportunities of innovation: quantitative, qualitative, and mixed methods.

Quantitative methods

Quantitative research is the systematic empirical investigation of social phenomena via statistical, mathematical, or computational techniques [56]. The major characteristics of quantitative research are a focus on deduction, confirmation, theory/hypothesis testing, explanation, prediction, standardized data collection, and statistical analysis [57]. Quantitative data is used, and is any data that is in numerical form [56]. Data gathering by surveys with closed questions or Likert-type scales lends itself well for quantitative research [53].

There is a wide range of analytical tools available for analyzing quantitative data. For the identification and assessment of possible introduction barriers quantitative methods are less suitable than qualitative methods. This is because gathering data for quantitative research mainly relies on closed questions. Subsequently quantitative methods lead to results biased by the researcher’s selection of identified barriers [53]. This is not desirable when one want to explore and discover possible introduction barriers. Therefore, quantitative methods and tools will not be further elaborated.

Qualitative methods

The major characteristics of qualitative research are induction, discovery, exploration, theory/hypothesis generation, the researcher as the primary “instrument” of data collection, and

qualitative analysis [57]. Qualitative methods are suitable for the analysis of information gathered through interviews or by focus groups. Qualitative research methods try to identify themes and patterns from the interview data, which is exclusive for that particular set of participants or setting. Several tools are available which can be used in qualitative research. For the identification of the forces of entry categorical or thematic coding, descriptive statistical analysis, content analysis, and constant comparison methods are used most often [53]. A short description of a few qualitative tools will follow below as an example. Due to time constraints it is not possible to address them all. The selection is limited to the tools that are used most often in qualitative research in the health care sector.

Categorical or thematic coding is used as a data retrieval tool from a text. It is used to classify text according to a theme, so when performing the analysis, it is easy to retrieve all passages that relate to a given topic. The coding process involved recognizing an important moment and encoding it prior to a process of interpretation. A “good code” captures the qualitative richness of the phenomenon. Encoding the information organizes the data to identify and develop themes from them. A theme is defined as a pattern in the information that at minimum describes and organizes the possible observations, and at maximum interprets aspects of the phenomenon [58]. Descriptive statistical analysis is a tool mainly used for analyzing qualitative survey data. The tool focuses on the exhaustive measurement of population characteristics. Of a defined population each member is assessed and from it a summary value, such as a mean or standard deviation is computed [53].
Content analysis is a tool that can be used to analyze the content of an interview text. It is a method by which the text is condensed and abstracted to be able to categorize statements of the interviewees. The words or statements of the interviewees which relate to the same central meaning are labeled, and form a so called content unit. These units are sorted into categories and if necessary sub-categories. The categories must be exhaustive and mutually exclusive [59].
The constant comparison method is a useful tool for investigating patterns in data over time. By comparing, the researcher is able to do what is necessary to develop a theory inductively by categorizing, delineating categories and connecting them. New data is gathered for the categories and compared with the old data. In this way it is possible to answer questions that have risen from the analysis and to reflect on previous data. The questions concern interpretations of phenomena as well as boundaries of categories, assigning segments or finding relations between categories. This cycle of comparison and reflection can be repeated several times [60].

Mixed methods

Mixing qualitative and quantitative methods is used to expand the scope, and deepen the insight of studies. Many combinations are possible, which combinations and how combinations should be made is point of debate [61]. How a research would be designed depends on which part the emphasis lies, the qualitative or quantitative part, and whether one wants to conduct the phases concurrently or sequentially [57].
Using mixed method designs for barrier analysis may yield more trustworthy results [53], and can answer a broader and more complete range of research questions [57]. However, it can be difficult to carry out both qualitative and quantitative research by a single researcher. Using a mixed method is more time consuming and details of mixing need to be worked out [57].

4.0 Method

This chapter will describe the methods that are used in this research for the early MTA of the µDtect. First the main method of data collection used in this research is described; the semi-structured face to face interviews (4.1). This is followed by four paragraphs which show the four parts of the early MTA; the clinical case analysis (4.2), the stakeholder analysis (4.3), the early economic evaluation (4.4), and the forces of entry analysis (4.5). For each part of the analysis the corresponding sub-question, specific details on the data collection method and method of analysis are described. All the information from these four parts is brought together and analysed to get to an answer on the main research question. The method used for this will be described in the paragraph early medical technology assessment (4.6).

4.1 Interviews

The µDtect is still in a development phase and therefore empirical data may not be available for every aspect. Expert opinions are used for the data which is not empirically available. Gathering expert opinion data is done by means of semi-structured face to face interviews. Structure is required to gather information about every topic. The topic needs to be explored, possibilities to be identified and opinions to be gathered. Open ended questions give room for exploration, and allow probing in order to pursue an idea in more detail [62].
The selection of experts is based on whether the person works with clinical microbiology identification technology and/or is involved in the process of acquiring medical technology in a hospital or laboratory. The number of interviews is based on whether the interviews provide new information or not. End point for initiating new interviews is when several interviews do not yield new insights. This does not guarantee that all possible data was gathered, but indicates that the exploration in the areas has been reasonably done.

All the interviewees were presented the same information: a short summary of the workings and possibilities of the µDtect and a document that went more into technical details of the µDtect.
An audio recording device was used during the interviews. These recordings were converted to written documents at a later time.

4.2 Clinical case analysis

The main goal of this research is to give a recommendation on the clinical setting and the form in which the µDtect would have the highest expected clinical and commercial value. The first step towards reaching this goal is by exploring and assessing the current clinical market and the clinical potential of the µDtect.
The goal of the clinical case analysis is to identify and assess possible markets for a new medical product. Based on the identified potential market the competitors are identified as well as their advantages/disadvantages. Therefore, clinical case analysis does structure the product features and product potential, without quantifying them. Performing a clinical case analysis gives answer to the second sub-question of this research:

Which are potential settings within the clinical health care market for an implementation of the µDtect and identification of which bacterial pathogens are of importance within these settings?

Data collection

The data for the clinical case analysis will be gathered through semi-structured interviews and a literature search. The reasons for using semi-structured interviews have been described above (4.1). The field of clinical microbiology is complex. Interviewees who did not work directly in the clinical microbiology laboratory indicated that they did not possess the knowledge to answer the questions for the clinical case analysis. Therefore, the selection of interviewees for the clinical case analysis was limited to microbiology physicians and the head of microbiology laboratory unit.
The following questions were asked during the interviews with respect to the clinical case analysis:

- How does the current clinical microbiology identification procedure look like and what are the strong and weak points of this procedure?
- Where lay the opportunities in the current clinical microbiology identification pathway for the µDtect?
- Which pathogens or microorganisms are essential for the µDtect to be able to identify?
- What are potential clinical markets outside the Dutch clinical market and why?
- What are the main competing technologies for the µDtect, now and in the future?
- What are the advantages and disadvantages of the competing technologies?

The answers were recorded with an audio device and documented at a later time.

Method of analysis
Distilling information from the written data of the interviews was done by thematic coding. Passages were highlighted which related to the following themes: possible markets for the µDtect, possible (development) opportunities for the µDtect, possible competing technologies. Codes were given to these passages based on the essence of the passage. Theme analysis was used for ordering the codes in categories. The main categories were based on the aims of the clinical case analysis: possible markets, possible opportunities, and possible competitors.
To get deeper insight, background information was gathered based on the codes distilled from the interviews. This background information was gathered from scientific literature and documents received from hospitals and institutions. For searching the literature Google Scholar is used. The codes and categories from the theme analysis were used as search terms. Only English scientific papers of the year 2000 or later were selected.

4.3 Stakeholder analysis

When a new product is intended to be introduced to the market it is important to know “who or what really counts” [28]. Answers to questions like: “Who has influence on the introduction or usage of a medical technology?” and “To what degree does a certain stakeholder have influence on a possible introduction?” provide valuable information. A stakeholder analysis provides an answer to these questions and therefore an answer to the third sub-question:

Who are the stakeholders and what is their function and influence when introducing or using a clinical microorganism identification technology?

The stakeholder analysis is conducted with respect to two processes: introducing a new clinical microbiology identification technology, and using the identification technology after introduction. These two processes are both relevant because they have to a large extend influence on the clinical

and commercial success of the µDtect. With success is meant that the µDtect will be implemented in the current clinical practice, and used routinely.

Data collection

For the identification of potential stakeholders semi-structured interviews are conducted. The selection of interviewees is based on the (possible) involvement in the process of acquiring new medical technology and/or the usage of microbiology identification technology. By selecting stakeholders from different steps within these processes the chance is reduced that certain stakeholders are failed to be identified.

The questions asked during the interviews for the stakeholder analysis are:

- How does the process of acquiring new medical technology look like and who is in what way involved?
- Who would have influence on the usage of the µDtect when it is implemented in the clinical microbiology identification process, and in what way?

The answers were recorded with an audio device and documented at a later time.

Method of analysis

Thematic coding was used for distilling possible stakeholders from the interview documentation. The identified stakeholders and the reason how they have influence are compiled in a table. For the process of acquiring new medical technology and the process of using a microbiology identification device, a classification of the possible stakeholders is made. This classification is done based on a framework designed by Mitchell [30]. The strength of the framework of Mitchell is that it does not only classify possible stakeholders, but provides an indication of the amount of influence of certain stakeholders as well. For the e-Nose company this is valuable information when introducing the µDtect to the market, because it gives an indication of which stakeholders are essential to convince of the use of the µDtect.

The stakeholder analysis concludes with an assessment of the implications for an introduction of the µDtect. The information of which stakeholders are essential and the accessability of these stakeholders are combined. Combining these two elements gives an indication of where to invest time and resources for convincing certain stakeholders of the use of the µDtect.

4.4 Early economic evaluation

For the eNose company it is valuable to know which decision criteria play a role in the decision of acquiring a new microbiology identification device. Based on the information it would be possible to focus the development of the µDtect on the aspects that are deemed important. The relevant stakeholders, from whom to elicit the importance of the decision criteria, are identified in the stakeholder analysis.

The performance of the µDtect on these decision criteria can be compared to the performance of competing technologies, which are identified in the clinical case analysis.

These two parts; Identify the decision criteria and their importance and investigate the performance of the µDtect compared to competing technologies, are the main parts of the early economic evaluation. This early economic evaluation gives answer to the fourth sub-question of this research:

What are the critical success factors and how well does the µDtect perform on these factors compared to competing technologies?

Multiple criteria decision analysis

The decision of acquiring new identification technology is based on qualitative and quantitative criteria. An MCDA is conducted in order to give insight in this decision. The methods used within the MCDA are described below.

Decision criteria

The identification of the decision criteria is done through semi-structured interviews. The first three interviews were used for the identification of relevant decision criteria. A value tree is constructed from these criteria. Later interviews were used for checking the value tree on the completeness, operationality, decomposability, absence of redundancy, and the minimum size, as described by Keeney & Raiffa [44].

The important pathogens, which a microorganism identification device should be able to identify, were gathered from the clinical case analysis. These were not included in the value tree in order to limit the size of the tree. Performance on these pathogens is analyzed though, because it can give an indication to where the R&D of the µDtect should focus.

The relative importance of the decision criteria has been determined by the budget pie method. The allocation of points is a fast and intuitive way of eliciting preferences. Due to the limited amount of time available and the ease of use of the method, this method was preferred above other methods.

The value tree was not complete and available at the first three interviews, resulting in some missing values. A case wise deletion method would result in omitting a too large portion of the available data. Therefore, the data will be imputed based on the averages of the available data within that class, which will influence and reduce the variance. For this research we are interested in the mean only, to get a general idea of what is deemed important.

Measurement of performance

Some of the alternatives are still in development; complete and accurate data is not yet available for all alternatives within the literature.

Information found in the scientific literature was used when possible. If scientific literature was not available, expert opinions elicited from the interviews were used. Other documents, like product presentations were used when the other alternatives were not available, the downside of these documents is the possible bias. If none of the above was available estimations were made. These estimations are done based on comparable technologies, applications in other fields, or by reasoning. For the literature search the database Google Scholar was used with the following keywords singular or in combination: MALDI-TOF/MS, Raman spectroscopy, Real time PCR, Lab on a chip, performance, costs, maintenance, implementation, ease of use, usage, and training. Only articles from the year 2000 or later were considered.

The data will be presented in a performance matrix and transformed to an interval scale. This transformation is done based on a linear value function. The linear value function is chosen because of the available data and time constraints. For the direct rating or a comparison based rating

information about the performance of all alternatives on each decision criteria should be known during the interviews. During the interviews the decision criteria and alternatives had yet to be determined. Due to time constraints a second round of interviews was not possible. Therefore, a linear value function is chosen which is suitable for providing an indication of the performance of the µDtect compared to its competitors.

Early economic evaluation

For the comparison of the alternatives on their overall performance the total weighted utility scores are calculated. Averages are taken if the performance was given with an interval.

To get an indication of how robust the outcomes are a sensitivity analysis is conducted by means of a scenario analysis. The selected scenarios are: the worst case scenario, the best case scenario, and the outstanding clinical performance scenario. In the worst case scenario the lower bounds of the performance measures for the µDtect are used and the upper bounds of the alternatives. In the best case scenario the upper bounds of the µDtect and the lower bounds of the alternatives are used. In the outstanding clinical performance scenario it is assumed that the µDtect performed well on the clinical aspects.

These scenarios give insight in the robustness of the data and what influence intensive R&D has on the position of the µDtect in the Dutch clinical microbiology market.

4.5 Forces of entry analysis

Forces of entry can hinder an introduction of a new technology or product to a market, but can be turned into strengths as well. Identification of the forces of entry in an early stage of development enables the producer to act on them. When the possible forces are known, a strategy can be developed to avoid the force of becoming a barrier and to possibly be turned into an advantage. The forces of entry analysis will provide an answer to the fifth sub-question:

What are the forces of entry and how do these affect a possible introduction of the µDtect?

Data collection

As Cochrane [53] stated semi-structured interviews with open ended questions serve an exploratory function and therefore enable the revealing of unanticipated forces of entry. Experts who are working with microorganism identification techniques and experts who are involved in the process of acquiring new medical technology are selected for the interviews. Their expertise can give insight into the aspects that can become introduction barriers.

Microbiology physicians are selected because they have experience with microorganism identification techniques and have insight in the required technological aspects. These technological requirements can be a barrier of entry. Experts who are involved in the process of acquiring new medical technology are selected because they can give insight in the organizational and social aspects, which potentially contain different forces of entry. Together they should give a complete view of the possible forces of entry which can influence the introduction of the µDtect.

Experts from peripheral hospitals, independent microbiology laboratories, and a microorganism identification technology producing company were interviewed. These interviews were recorded with an audio-device and documented at a later time.

Method of analysis

For the analysis of the forces of entry qualitative methods are used. Qualitative methods are suitable for discovery and exploratory research (Johnson, 2004). Identifying and analyzing possible forces is exploratory in nature. Thematic coding and content analysis are used for the identification categorization of the possible forces.

Thematic coding is used for distilling the possible forces of entry from the written interview documents. All passages which contained possible barriers or clinical requirements were highlighted. These passages from all the interviews were transferred and compiled into one single file.

A content analysis was performed to sort the responses of the interviewees. The responses, selected by the thematic coding, were labeled. These labeled responses were sorted in sub categories. These sub-categories are the possible introduction barriers or opportunities and are ordered based on the classification of Herzinger [15].

4.6 Early medical technology assessment

The early MTA is a combination of methods that allow for more informed decision making in earlier stages of product development. Decisions on investments in R&D may require formal assessment methods, as do decisions on specific features in new medical products or decisions on minimal clinical performance to be able to compete with existing products [11]. This early MTA combines and assesses the information provided by the clinical case analysis, early economic evaluation, and the forces of entry analysis. The goal of the assessment is provide an answer on the question:

In what setting in the clinical market should the µDtect be situated and which direction of development should be aimed at in order to attain the highest expected clinical and commercial value?

Data gathering

The data for the early MTA will be provided by the clinical case analysis, the early economic evaluation, and the forces of entry analysis (Figure 8).

The clinical case analysis provides information about potential markets for the µDtect as well as information about important or essential pathogens that a clinical microbiology identification device should be able to identify.

The early economic evaluation provides information about the clinical needs and the performance of the alternatives. The forces of entry analysis provides information about the possible critical barriers and the opportunities that the market provides.

Method of analysis

The results from the four parts of the early MTA are compiled. By synthesis the data is structured into the strengths, weaknesses, and opportunities for development of the µDtect. Knowledge about the strengths of the µDtect can aid in the selection of potential markets and within the clinical setting for the µDtect. Weaknesses can indicate whether more research and development is needed, or which setting or potential clinical markets will be hard to enter due to the weaknesses. The opportunities for development provide the possibilities in which development can aid to improve the expected clinical and/or commercial value.

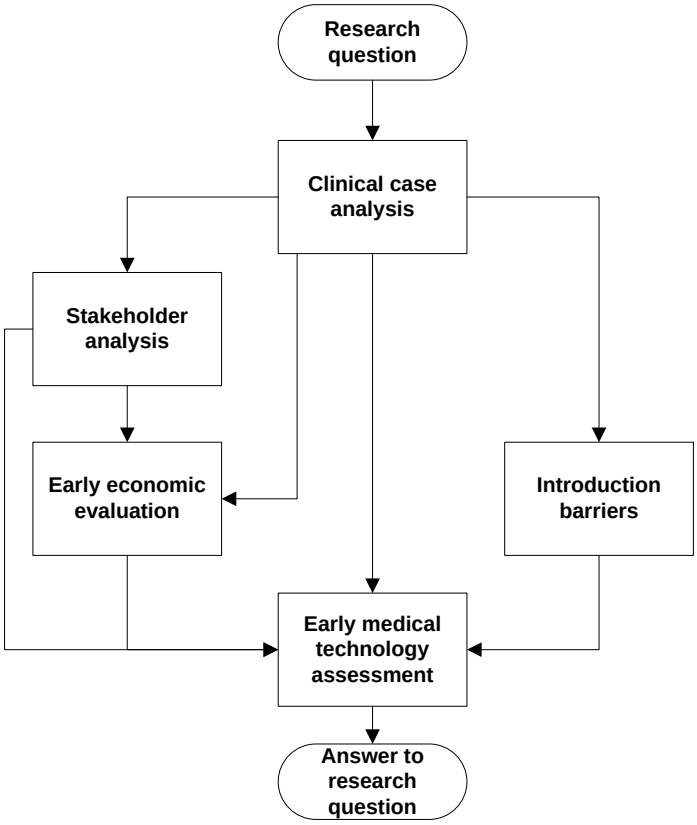
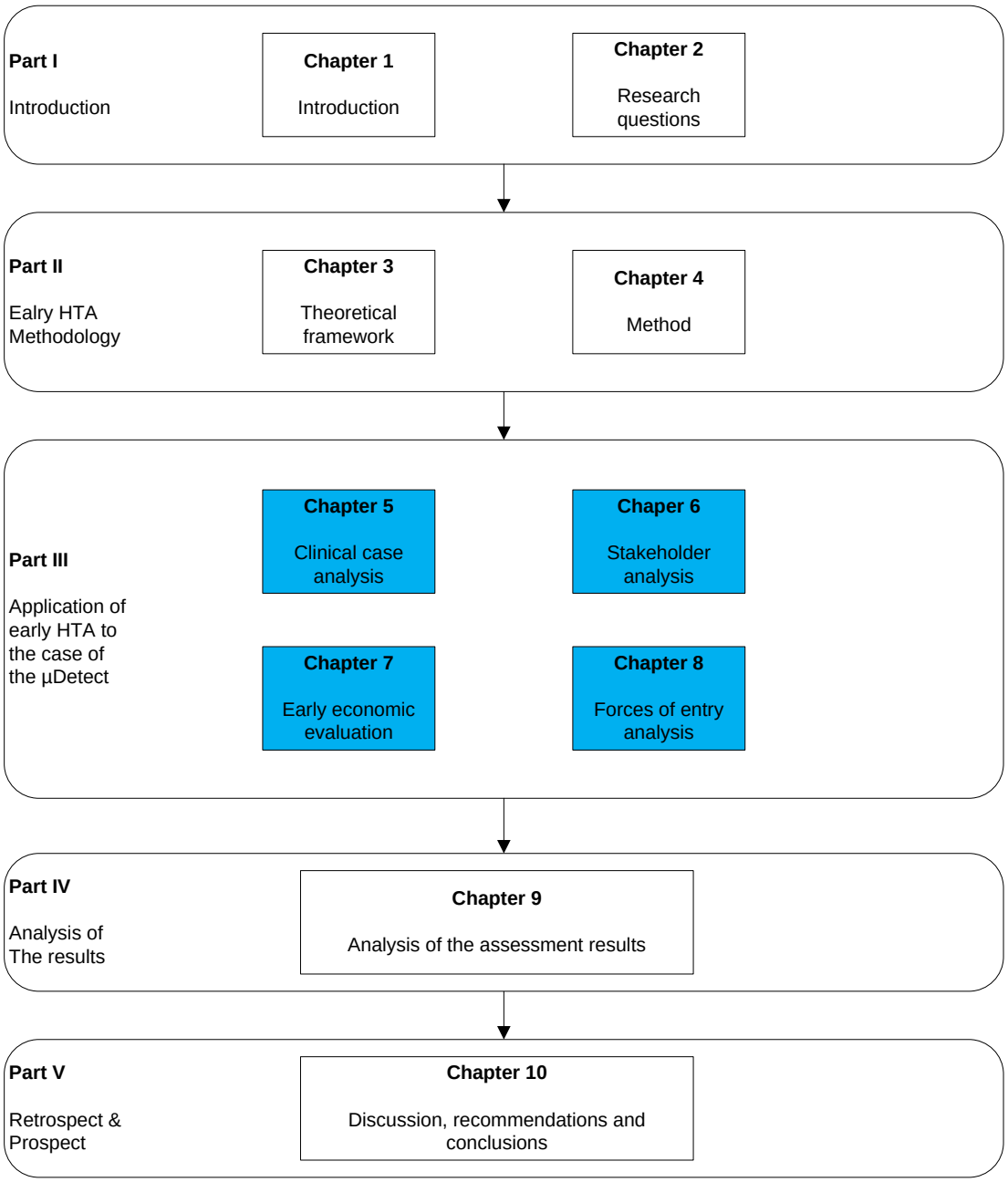


Figure 8: early MTA research design

Part III

Application of early health technology assessment to the case of the µDtect



5.0 Clinical case analysis

This chapter the clinical case analysis will be presented. For the clinical case analysis it is assumed that the state of the art of the current clinical market is known, this is described in paragraph 5.1. This will function as a starting point from where the clinical case of the µDtect will be explored (5.2). The chapter will conclude with the implications of the results for the µDtect (5.3).

5.1 Clinical state of the art

A prerequisite of performing a clinical case analysis is that there is a detailed overview of the clinical state of the art including existing products and their main advantages and disadvantages [11]. The current process of microorganisms within a clinical laboratory will be described first which is currently the state of the art of the Dutch clinical market .

Blood sampling

Blood samples are taken from patients in the hospital or at specialized outpatient blood sampling units. The blood sample will be withdrawn directly into a blood culture bottle. The most commonly used culture bottles in the Netherlands are the Bactec™ culture flasks. These flasks contain a medium which provides a nutritious environment for micro-organisms. At the bottom of the flasks is a Ph indicator.

Transportation of the sample

The sample is transported to the microbiology and immunology laboratory. The time from when the blood is taken to when it arrives in the laboratory is dependent on the distance and on the time the sample is taken. When the laboratory is situated within the hospital where the sample is taken it can get there within the hour, when the sample comes from an external hospital or post it can take up to 12 hours before the sample arrives. Transportation from external hospitals or post is normally done once a day.

Incubation of the blood sample

The blood sample is placed in an incubator. The incubator keeps the sample on a temperature of 95 degrees Fahrenheit (35 degrees Celsius), and is constantly swirling the sample. These conditions provide an optimal growth conditions for microorganisms. Becton Dickinson Company and bioMérieux are the main providers of blood culture systems which are widely used in the Netherlands [63]. The flasks will incubate for 8-12 hours. When micro organisms are present in the sample the indicator at the bottom of the flask will change color due to the increase of carbon dioxide, which is produces by the metabolism of the microorganism. The culture system detects the color change and gives a signal that the sample is positive.
Positive samples will be taken out and be handled for further analysis. Negative samples will be kept for a few days to confirm that there are no microorganisms present. The diagnosis of the negative samples, which encompasses about 90% of all the samples, is not communicated to the attending physician.

Gram staining

When the presence of a microorganism is detected a gram staining is conducted. Gram staining is the first step in the classification and identification of the microorganism. It is based on the fact that some species can be easily decoulorized with organic solvents whereas others resist decolourization.

These colouring characteristics correlate with important physiological and chemical characteristics of the cell and with it the susceptibility to antibiotics [64]. The colouring makes it possible to identify the shape (spherical- or rod-like) and the biochemical features of the micro organism (Gram positive, Gram negative), and therefore makes it possible to classify the organism into one of four groups. This staining takes less than a minute.
If the results indicate that the patient should get other antibiotics than it currently receives, the microbiology physician will communicate the results to the attending physician.

Culturing and susceptibility testing
The goals of testing are to detect possible drug resistance in common pathogens and to assure susceptibility to drugs of choice. The susceptibility tests are performed by applying bacterial inoculums to the surface of agar plates. An agar plate is a Petri dish that contains a growth medium and possible selective growth compounds, such as antibiotics. The microorganisms are cultured by incubating these plates for several hours (4 hours minimum, but often overnight). The susceptibility profile can be determined based on the growth of bacteria. One plate will be used to cultivate separate colonies, which will be used for the identification of the micro organism.
Preparation and streaking of the agar plates is often done by hand, although there are also fully automated systems available like the Copan's Wasp®. There are automated systems available that can test for susceptibility. The Phoenix (BD Diagnostics), the VITEK (BioMérieux), the Sensititre ARIS (Trek Diagnostics Systems) are examples of such systems, although manual preparation is still required [65].

Microorganism identification
The final step is the identification of the microorganism. The state of the art is the MALDI-TOF /MS, which stands for Matrix Assisted Laser Desorption-Ionization (MALDI) Time-Of-Flight Mass Spectrometry (TOF/MS). It is a rapid identification method that can identify bacteria in several minutes, provided that sufficient bacteria have been collected [7]. To get sufficient bacteria the separate colonies cultured on the agar plates are used. It is possible to do perform an identification test with the MALDI-TOF/MS directly after the detection, but there will be a higher chance that the identification is not successful [66]. Therefore it is standard procedure to perform the identification after cultivation.

5.2 Clinical case analysis of the µDtect
The data is collected by means of semi structured interviews with experts. The information for the "intended application" (5.2.1) and de "possible advantages" (5.2.2) are gathered through interviews with personnel of the eNose company.
For the "target market" (5.2.3) seven experts from the field of microbiology and immunology were selected. These consisted of six microbiology physicians and one unit head of microbiology and immunology laboratory. Personnel in management and supporting functions are asked about the possibilities for the µDtect, but they announced that they did not have the knowledge to give a well founded answer.
Three of the physicians as well as the unit head work at laboratories which are part of a peripheral hospital. Two physicians work at independent laboratories and one works as a R&D director for BioMérieux. The comparator interventions (5.2.4) are selected based on the expert interviews. The

advantages and disadvantages of the comparator interventions have been compared to those of the µDtect to get an indication of the expected clinical outcome (5.2.5).

5.2.1 Intended application/product

The µDtect is designed for identification of pathogenic microorganisms with the focus on bacterial microorganisms. The µDtect can be used with Bactec™ culture flasks which are common use within the clinical microbiology laboratory.
The µDtect is designed to be applied for routine testing within a microbiology laboratory, in remote areas, or at the point of care.

5.2.2 Possible advantages

Faster identification

The µDtect is able to identify certain micro-organisms effectively during the incubation step [10]. Currently it is common practice to perform the identification after cultivation, because then pure colonies of the microorganism are available. Therefore, diagnosing with the µDtect could speed up the identification considerably. Advantage of faster identification is that the antibiotic treatment can be streamlined at an earlier time, which reduces the risk of undesired side effects for the patient and on the micro-flora.

Less follow-up tests

The µDtect can identify micro-organisms before gram staining and susceptibility testing. Upon identification by the µDtect a gram staining will be redundant. Susceptibility testing can be performed with more focus, which has the potential to reduce the number of tests required. No further identification tests are required.
The reduction of tests may result in a reduction in hands on time, which could lead to lower costs.

Identification on location

The µDtect can function fully stand alone, it just requires a power source. Therefore it has the ability to perform identifications at sites outside the microbiology laboratory. It can be used in remote areas, which do not have access to a laboratory. Other possibilities are to use it at the point of care, such as the general practitioners office, the intensive care or at the outward patient post.

Low investment costs

Current microorganism identification devices, like the MALDI-TOF/MS, are expensive to acquire. The µDtect will be significantly less costly and therefore may have potential to be applied within developing countries or smaller hospitals.

5.2.3 Target market

To determine the development direction of the µDtect it is essential to know which market to target. In other words who are the intended buyers and users of the µDtect. For the identification of target markets µDtect experts are asked where the µDtect has potential. The results are shown in table 3. The numbers correspond with interviewees. Number 1-6 are microbiology physicians, number 7 is head of the bacteriology and immunology unit.
Three potential markets are identified. Seven respondents identified a microbiology laboratory in Western countries as a target market. Western countries have high tech microbiology laboratories. Integrating the µDtect technology with the current available technology could increase the market

potential of the µDtect within the Western market. Three microbiology physicians identified microbiology laboratory in developing countries as a target market. Developing countries are not the poorest countries, because there, determination of illnesses is done based on the clinical image. Specific identification of the bacterial pathogen involved will provide information which cannot be acted upon, cause of the absence of specific antibiotics and knowledge. Two microbiology physicians indicated that the µDtect can be applied and add value in remote areas, as long as it was within a laboratory. The respondents did not see potential in application of the µDtect outside of a laboratory. Main reasons were that the field of microbiology is complex and skilled people are required to judge the results. After identification by the µDtect, susceptibility testing is still required, which are done in a laboratory. Performing these process steps on two separate locations is not desired. The potential application of the µDtect at the IC and the general practitioners office are described below.

Intensive care

Interviewees were asked whether applying the µDtect at the intensive care (IC) or at the general practitioner (GP) would be an option which could add clinical value. Placing the µDtect at the IC provides the possibility to start diagnosing blood samples of critical patients. This would abolish the transportation time from the IC to the laboratory. The respondents did not see potential in placing the µDtect at the IC. Main reasons were that the people working at the IC do not have the time to perform an additional task which lies outside their expertise. When identification was done at the IC, the sample still has to travel to the laboratory for susce[67]ptibility tests. This would result in a little earlier detection and identification, but an increased workload at the IC and less experienced people working with the blood samples.

General practitioner

The GP makes requests to the laboratory for tests. Therefore, placing the µDtect at the GP's office could provide faster results and a lower workload for the microbiology laboratories. The samples the GP sends for testing are mainly urine samples. When the GP suspects that a patient is septic, he/she will be directed to the hospital. It is not common that a blood sample is taken by a GP, this is mostly done at the hospitals. Therefore, placing the µDtect for blood analysis would not be of added value. When the µDtect is able to analyze urine samples it could be of added value for the GP. It then must give a fast, clear result and even give a suggestion on what antibiotics the GP should prescribe.

Target place	Reasons and remarks
Laboratory in Western countries (1-7)	Faster time to identification is of added value (1-7) Preferably in combination with an already available technology for additional information. Laboratories do not likely acquire a new separate identification device for a minor reduction in the time to identification (3, 6-7). On at least a scale of 400 or more bottles simultaneously (4,5) The µDtect has to be considerable (more than 12 hours) faster than the current procedure (1). Has to be at least as accurate as the MALDI-TOF/MS (2)
Laboratory in developing countries (3-5)	Not the poorest countries, they work with the clinical image. Assessing visible symptoms. Determination will be a step too far. (3-5)
Remote area's (5-6)	Field hospitals, Doctors without borders, small remote hospitals

Table 4: Potential target clinical markets

Target pathogens

There is a broad spectrum of pathogens and micro-organisms. The µDtect is not yet able to identify all of them with high accuracy. Research and development can improve the identification capabilities of the µDtect. To be able to direct the development it is valuable to know which pathogenic microorganisms are important to be able to identify. Experts are asked what pathogenic microorganisms the µDtect should be able to identify. The results can be found in table 4.

The broader the range of pathogenic microorganisms the µDtect can identify the better, although four microorganisms are marked specifically as important by several respondents. The Staphylococcus Aureus, Staphylococcus Epidermidis, Eschericha Coli, and the Streptococcus Pneumoniae are important pathogenic bacteria to be able to identify. Mainly because these are most frequent, most virulent, or can have a serious impact.

One respondent responded that the µDtect can add value when it can differentiate in an early stage between four main groups. These groups are based on the required therapy. Aiming for exceptions (hard to detect with the current practice) can also provide an added value, especially when it is a highly virulent pathogen.

Essential/Target pathogens	Reason
Staphylococcus Aureus (3-4)	Most virulent cause of disease. (3)
Streptococcus Pneumoniae (3-5)	Causes the pneumonia. (3) Important to identify for oncology patients, IC patients and patients with an artificial joint.
Eschericha Coli (3-5)	High frequency. (3)
Staphylococcus Epidermidis (4-5)	This is the main source of contamination. It lives on the skin and can get from the needle into the sample. But it still can be a serious cause, especially for oncology patients, IC patients and patients with artificial joints (4-5).
Broad scala of pathogens (5)	The broader the range of pathogenic microorganisms the µDtect can identify the better.
Aim for the exceptional	When it can detect the exceptions it has a better chance to get on the market.

pathogens (2,6)	
Top 10 pathogens (5)	The broader the range of pathogenic microorganisms the µDtect can identify the better.
Differentiation between 4 groups (1)	These groups differ in required therapy (antibiotics). The groups are 1: Eschericha Coli, Klebsiella, Proteus 2 Enterobacter, Citrobacter, Pseudonomas 3 Staphylococces, Streptococcus 4 other
Urine/other samples (1,4-6)	The µDtect must be capable of determining how many micro-organisms of a certain species are available. The dominating bacterium (factor 10) is probably the cause of the disease/infection.

Table 5: Important pathogenic microorganisms

5.2.4 Competing technologies

The competing technologies with their advantages/disadvantages are shown in table 5. Not all technologies are fully developed yet as micro-organism identification techniques, but they have potential to become players in the field of microorganism identification.

MALDI-TOF/MS

The MALDI-TOF/MS is currently the state of the art in a clinical microbiology laboratory. After incubation and culturing of the sample the MALDI-TOF/MS can perform a rapid identification of the micro-organisms present in the sample. In short the MALDI-TOF/MS works as follows.

The sample is spotted onto a MALDI-TOF sample target with appropriate matrix and allowed to air dry at room temperature. Then, the plate is inserted into the mass spectrometer; the dried matrix-sample mixture is bombarded with a laser to create gas phase ions that are then pulsed into a flight tube. The ions are separated according to their molecular weight after migration in an electric field. The species of interest are identified by their mass/charge ratio [67]. The results are compared with a database. This database contains mass spectral fingerprints of the known micro-organisms.

The MALDI-TOF/MS can identify micro-organisms with high accuracy and for a broad spectrum of microorganisms [66-69].

Raman Spectroscopy

Raman spectroscopy is a technique that can be used in several medical settings of which the rapid identification of pathogenic microorganisms is one [70]. The technique is based on the scattering of light. When a beam of light (laser) hits a molecule then this molecule will scatter and alter the frequency of light. Based on this scattering pattern the molecule or microorganism can be determined [71].

The identification can be performed after the cultivation step from cultures collected from agar plates. There are several devices that make use of Raman spectroscopy technology, but it is not yet widely implemented in a clinical environment [70]. The reference database has to be extended for all the different microorganisms for it to be suitable as a routine identification technique in a clinical biology laboratory [14, 72].

Real time PCR

PCR stands for Polymerase Chain Reaction which is a method to multiply DNA in samples with the use of primers. Real time PCR is a method that can identify DNA during the PCR. The multiplying of the DNA happens by use of a primer-probe. The label of this primer becomes visible when the

primer-probe is used. This release of the label emits light of a certain frequency. The more DNA available, the stronger the signal is. From this signal strength over time, the original concentration of DNA present in the sample can be calculated. The real-time PCR make it possible to perform a rapid identification. Although, specific primers need to be used for specific DNA, therefore only a focused search is possible [8].

Lab on a chip

The lab on a chip (LOC) consists of independent (micro-) fluidic channels. These channels are used as measuring channels which enable the simultaneous detection of different analytes. This is done by pre-coating each measurement channel with a unique receptor layer. This receptor, e.g. an antibody, specifically binds one type (or class) of micro-organisms, such as viruses, bacteria, yeast, fungi, or small parasites. This makes rapid identification possible [73]. The LOC can be used at the point of care

A lot of research has been done at the LOC and the technology seems promising. However, it is still in the development stage and more research is needed to make the technology commercially ready [74]. There are devices and prototypes available which are capable of analyzing the presence and concentration of microorganisms in blood samples.

Competitors	Strong points	Weak points	Source
MALDI-TOF/ MS	• High accuracy • Broad spectrum • Easy to use • Fast identification • Low operation costs	• High purchase price • Sample preparation needed for best result	[66, 68-69](
Raman spectroscopy	• Can determine whether bacteria come from the same source • High accuracy • Easy to use • Fast identification	• Test are expensive • Database not yet complete • Need sample preparation	[14, 72]
Real time PCR	• Wide range of identification and quantification • High sensitivity • Rapid identification • High precision	• Can only search known pathogens • Need to target specific pathogens • Mutations can lead to false positives • High start-up expense	[8, 75-76]
Lab on a chip	• Easy to use • Small sample needed • No extensive culture process needed • Point of care • Rapid analysis	• Chip targets specific known organisms • Sample loss • Contamination	[73, 77]

Table 6: Strong and weak points of competing technologies

5.3 Implications for the µDtect

According to the respondents the µDtect have the highest expected potential within a microbiology laboratory. These laboratories can be situated in Western countries, developing countries, or remote areas.

For the Western market important bacterial pathogens are the Staphylococcus Aureus, Staphylococcus Epidermidis, Eschericha Coli, and the Streptococcus Pneumoniae. Being able to identify these effectively increases the clinical potential of the µDtect and may even be a requirement. For developing counties and remote areas the bacterial pathogens which are important may differ.

Four potential competitors of the µDtect are identified with their strengths and weaknesses. These strengths and weaknesses are compared to those of the µDtect without quantification. This provides a first indication of the opportunities and treats for the µDtect within the Western market. The results are presented in table 7.

	µDtect	MALDI-TOF/MS	Raman spectroscopy	Real time PCR	Lab on a chip
Operation costs	Low	Low	High	High	Unknown
Cultivation required	No	Yes	Yes	No	No
Ability to identify a broad spectrum of pathogens	Development required	Yes	Development required	Yes	Development required
Ability to diagnose broad spectrum of samples	Development required	Yes	Yes	Yes	Development required
Ability to quantify	No	No	No	Yes	No
Specific targeting required	No	No	No	Yes	Yes
In development stage	Yes	No	No	No	Yes

Table 7: Initial comparison of microorganism identification technologies

6.0 Stakeholder analysis

This part of the analysis is aimed to give an answer to the following sub question:

Who are the stakeholders and what are their needs and interests when introducing or using the µDtect as a pathogen identification technology?

The identification and classification of possible stakeholders is presented in paragraph 6.1. In the analysis a distinction is made between introducing and the usage of an identification technology. Identification of the stakeholders and in what manner and extend they influence the purchase process of an identification technology is presented in paragraph 6.2. In paragraph 6.3 the stakeholder analysis for the usage of microbiology identification technology is presented. This chapter will conclude with the implications for the µDtect.

6.1 Stakeholder identification

When dealing with the decision of adopting or using a medical technology, there are a lot of stakeholders that are potentially affected by the decision. Dependant on the technology in question, the number of stakeholders varies greatly. Once a clinician decides to use a new device or piece of technology, the clinician must often consider not only the impact on the patient and on the practice, but also what it means for the operational costs, health care policy, and the organization in which the clinician work [78]. The detection and identification of micro-organisms in a laboratory is not only done for the hospital where the laboratory is situated, but often for outside parties as well. This increases the number of stakeholders. Stakeholders who are involved in a technology adoption decision can be categorized into five groups. The groups are: the policy makers/regulators, the payer, the provider organization, the customer (Cain et al. refers to this as 'the patient'), and the vendor company [78]. The separation in the different categories can depend on the country where the adoption takes place. This is especially true for the payer and policy maker categories, which are strongly dependant on the finance system of the country in question. There are several finance systems for health care possible. With a social health insurance system, like in Germany, and France, the insurance companies can be seen as separate stakeholders. This counts for the private insurance companies (The Netherlands, United States) as well. The government, which falls under the category of policy maker and regulator, can be payer as well through a taxed based system for health care (Denmark, Sweden). The last group is 'direct payments' where the patient directly pays for his/her healthcare to the provider (Portugal).

6.1.2 Data gathering

Ten persons, working in eight different hospitals and/or laboratories, were questioned about the involvement of stakeholders. The compilation of respondents was as follows: Five microbiology physicians, two medical physicists, one head of the bacteriology department, one head of the healthcare technology department, and one manager of a microbiology and immunology laboratory. These persons were questioned during face to face conversations in Dutch hospitals and laboratories. The interviewees were asked to name the different stakeholders who would be involved during the purchase process of a new micro-organism identification technology and who were involved when using the new technology. The results of the stakeholder identification are presented in table 8.

6.1.3 Stakeholder classification

The policy makers and regulators

The category of policy makers and regulators encompass administrations and agencies that are responsible for protecting and promoting public health through the regulation and supervision of the quality and safety of medical devices. In the European Union this is done by the European Commission. When a manufacturer wants to produce or distribute a medical device within the EU it has to comply with a directive. For the distribution of a diagnostic device like the µDtect it has to comply with the Directive 98/79/EC on in vitro diagnostic medical devices. When the device complies to the directive it receives an In Vitro Diagnostic CE mark which is required to enter the European market. Many countries have similar institutes and regulations. In the United States of America the Food and Drug Administration (FDA) is responsible for the regulation of import of medical devices. Most countries have similar agencies, like China has the State Food and Drug Administration (SFDA).

The Payers

It is country dependant who is the payer for the medical care. In countries like Denmark and Sweden the bulk of the health care is paid through taxes. In this financial system the government is the stakeholder. With a social security system or when people have private health insurance, the payer are the insurance companies. In the Netherlands the price of a diagnosis is set by the Dutch Healthcare Authority (Nederlandse Zorg Authoriteit). It is incorporated in diagnosis related groups for which the prices are set. The insurance company has to reimburse the set price to the healthcare provider. The prices are based on the cost price of the diagnostic tests.

In the case of direct payment, where the patient pays him-/herself directly for the health care service, the patient is the payer. This is common in countries where a social security system or a government healthcare finance system is not in place and co-payments commonly apply like in for example Italy.

The provider organization

The category of 'provider organization' encompasses stakeholders who decide whether to provide the medical technology. During the identification procedure only the microbiological physicist and the analysts work with the identification technology. Where the physicist has the final responsibility and gives an advice to the requesting physician, managerial personnel are responsible for all the non clinical aspects of the laboratory.

In general, the purchase process in a hospital has the following structure. The process is initiated by the microbiological physicist. He/she makes a request for acquiring a new technology by means of presenting a business case. An investment commission looks at the request and brings out an advice to the hospital management. This investment commission consists of members of different departments in which, among others, medical specialists, financial specialist, members of the purchase department, clinical physicians, and biomedical engineers take seat. The composition is not fixed and can differ from hospital to hospital and from time to time.

The customers

The category "customers" consists of stakeholders who, by request, make use of the diagnostic technology. Most of the requests are internal and come from the physicians employed in the hospital the laboratory is connected to. External requests are done by other hospitals, general practitioners, food and consumer product safety authorities, and veterinarian physicians.

The vendor company

The category "vendor company" encompasses stakeholders which produce and sell the medical technology. For the µDtect this is the company eNose company. For the application of the Odocap®, the e-Nose company has a partnership with a flasks producer.

Competitors can have influence on the introduction of the µDtect and therefore they should be taken into account as stakeholders. In the case of the µDtect these are the producers of the MALDI-TOF/MS, Raman spectroscopy, the real time PCR and the 'lab on a chip'.

Policy makers/ regulators	Payer	Provider organization	Customers	Vendor company
European Commission **Food and Drug administrations**	Government Insurance companies Patient/customer	Microbiology physician Analyst Laboratory manager Department manager Hospital management Investment advisory committee Biomedical engineering department Purchase department	Patient/attending physician General practitioner Food and consumer product safety authority External hospitals Veterinarian physician	The eNose company Partners Competitors

Table 8: Identified stakeholders

6.2 Stakeholder analysis purchase process of the µDtect

The microbiology physician, laboratory manager, head of department, and the hospital management are the definitive stakeholders in the purchase process of a micro-organism identification device. Together they form the core of the decision makers. These key stakeholders base their decision on the advice that is given by the investment advisory committee and the purchase department. The purchase department sets its criteria based on the advice of the biomedical engineering department. These last three stakeholders are dominant stakeholders.

Analysts will use the technology and therefore may give advice to the physician. The approval of regulatory bodies and payers are conditions that have to be met. If not, the purchase process won't even start. After they are met, these stakeholders won't have significant influence on the purchase process.

Not all categories of stakeholders are present in the purchasing process. Dormant, demanding, dangerous and dependent stakeholders were lacking.

Type of stakeholder	Actors	Explanation
Dormant		
Discretionary	Analyst Regulatory bodies Payer	Analysts will be the main users of the technology, therefore their opinion is legitimate. Though, the Microbiology physician (definitive stakeholder) is in the lead for the initiation of the purchase process, therefore they lack the power. They do not have the urgency to change things because they are not responsible for the performance of the laboratory. Before the technology can be sold it needs to be approved by regulatory bodies. After the approval they cannot influence the purchase process. The purchase of a new technology should not have significant negative financial effects. The reimbursement of the use of the technology should be in place before the use of the technology.
Demanding		
Dominant	Investment advisory committee Purchase department Biomedical engineering department	The advisory committee makes a ranking and selection of all investment requests of the hospital. Therefore it has the power and the legitimacy to influence the purchase process. The purchase department makes a selection from comparative technologies and products. This selection is often based on the technical requirements set by the biomedical engineering department.
Dangerous		
Dependent		
Definitive	Microbiology physician Laboratory manager Head of department Hospital management	Microbiology physician and the laboratory manager are together responsible for the performance of the laboratory. Together they will build a business case for purchasing a new device. Dependent on the money involved with the investment the head of the department or the hospital management takes a decision whether or not to approve the investment. These stakeholders have the responsibility for the performance of the hospital/laboratory, therefore they have besides the power and legitimacy also the urgency to influence the purchase process.
Non-stakeholder	Patient Customers Vendors	The patient and other customers do not actively influence the purchase process for a diagnostic device placed in the laboratory. The technology is not visible enough to have a positive advertizing effect for the hospital. Vendors, including the e-Nose company, cannot actively affect the purchase process, assuming that they cannot pressure stakeholders in a certain direction. They solely have to provide the information needed by the stakeholders. The stakeholders make their decisions based on this information.

Table 9: Purchase process stakeholders

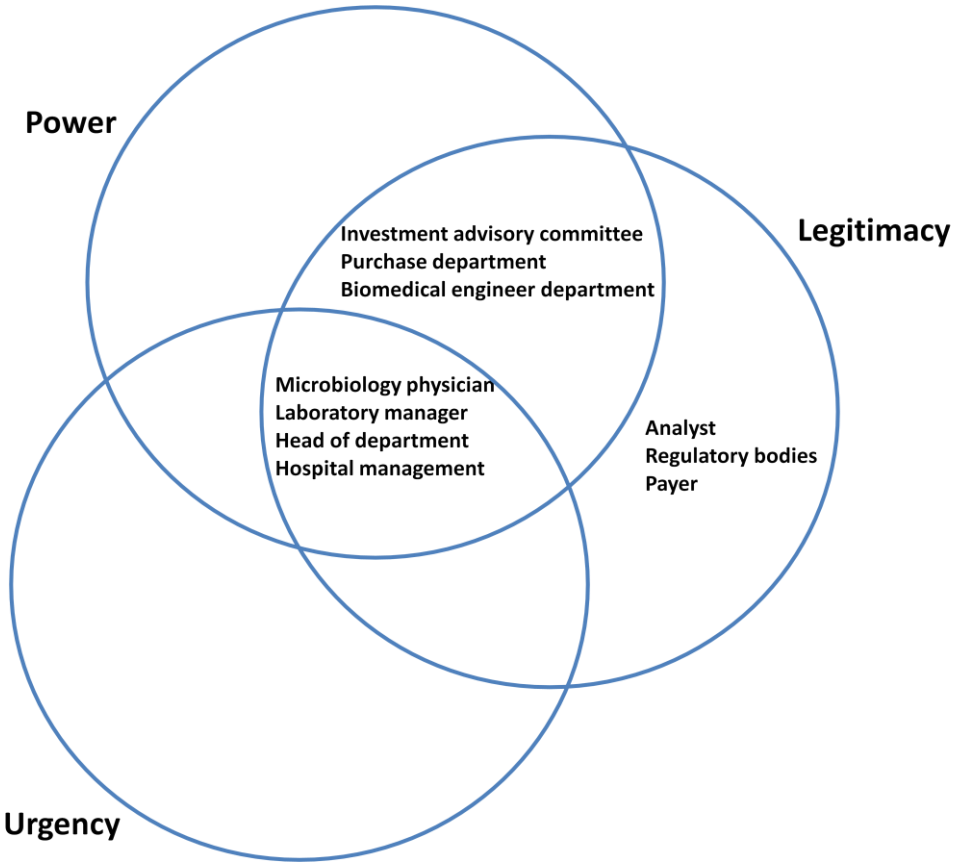


Figure 9: Purchase process stakeholders

6.3 Stakeholder analysis using µDtect

The stakeholders involved in deciding about actual using the microorganism identification technology can be categorized into five groups. Only the dormant and dangerous stakeholders are not present in the process. The most influential stakeholders for using the identification technology are the microbiology physician and the analysts. They are the direct users and can decide whether or not to use the device. The hospital management and the head of the department are dominant stakeholders. They oversee the usage of the product, and when problems arise they may become active. Customers and attending physicians are identified as dependant stakeholders. They have the urgency to get fast and reliable results, and the legitimacy to influence the usage by addressing (potential) complaints to the regulatory bodies and/or look for alternative laboratories.

Discretionary and demanding stakeholders, who possess only one attribute, do not have much influence on managers. Laboratory managers, biomedical engineering department, regulatory bodies and payers, are identified as discretionary stakeholders. They have mainly a consultative a monitoring role. When there are serious issues with the technology they can gain the attribute urgency, and therefore gain more salience. For the eNose company, identified as a demanding stakeholder, it is difficult to attain other attributes than urgency.

Type of stakeholder	Actors	Explanation
Dormant		
Discretionary	Laboratory manager Biomedical engineering department Regulatory bodies Payer	The laboratory manager and the biomedical engineering department are not directly involved in using the new identification technology. When the users are not satisfied with the performance of the technology they can have a consulting role. Regulators represent the stake of customers (dependent stakeholder) and may come into action when the performance of the technology is not adequate.
Demanding	e-Nose company	The eNose company earns money with each blood test done with the µDtect. Therefore it has the urgency that it is used, but they lack the power and legitimacy to influence the usage.
Dominant	Hospital management Head of department	These actors are not actively involved with the usage of the technology, but are responsible for the performance of the hospital. Therefore, may the technology cause problems, they may become active and use their power and claim.
Dependent	Attending physician Customers	The attending physician and the other customers do not directly use the technology, but they depend on the performance of it in order to do their own work. When the performance of the technology is not the required level they can influence the use by complaints (through regulatory bodies) or searching for alternative providers.
Dangerous		
Definitive	Microbiology physician Analyst	Microbiology physicians and analysts are the main users of the product and therefore definitive stakeholders.
Non stakeholder	Partners Competitors	Partners, provider of the blood culture flasks, do not care whether the µDtect or another identification device is used. As long as the culture flasks are used. Competitors have no influence on the usage of the identification device.

Table 10: Stakeholders usa process

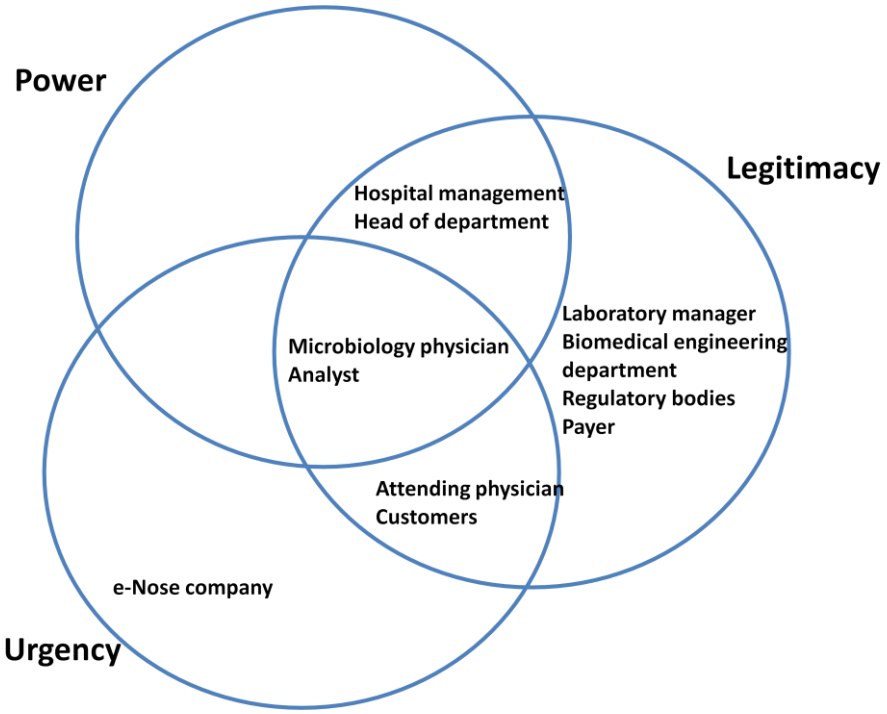


Figure 10: Stakeholders use process

6.4 Implications for the µDtect

Implications for the introduction of the µDtect

The purchase process starts with the microbiology physician and to a lesser extent with the laboratory manager. The eNose company can actively approach these key stakeholders in order to make the µDtect known and convince them of the added value. After that there is not much the e-Nose company can do in order to influence the purchase process.

The purchase process will continue internally. The investment advisory committee has an influential role in this process. It gathers all the investment requests from the hospital and ranks them. It advises the head of department and the hospital management, who will ultimately make the decision whether to invest or not. This advice is based on a business case that the physician provides. Several hospitals have standardized the format of the business case to make requests better comparable and to limit bias. Still the danger of bias remains because the investment advisory committee does not have a standard composition. The medical specialists seated in the committee can have a biased view of what is important, due to personal interests. This can be a danger as well as an advantage for the introduction of the µDtect. An overview of the approachability of the stakeholders of the purchase process is given in table 11. The stakeholders are categorized based on their salience. Stakeholders with high salience and which are approachable are for the eNose company relevant to focus their attention to.

	Hard to approach	Approachable
High salience	Hospital management Head of department	Microbiology physician Laboratory manager
Medium salience	Investment advisory committee Biomedical engineering department	Purchase department
Low salience	Regulatory bodies Payer	Analyst

Table 11: Approachability stakeholders

Implications for the usage of the µDtect

For using the µDtect there are only two definitive stakeholders, the microbiology physician and the analysts. For the eNose company, these two groups should be the main focus. Demands, complaints, and suggestions should be taken seriously. When these stakeholders are satisfied with the performance of the µDtect, the other stakeholder groups will probably not be able to influence the usage to a great extent.

7.0 Early economic evaluation

In this chapter the results of the early economic evaluation are presented. This evaluation is done by means of a MCDA. The goal of this chapter is to answer the fourth sub-question:

What are the economic and performance attributes critical for introducing a microbiology identification device to the market and how well does the µDtect perform on these attributes compared to competing technologies?

The results of the MCDA are presented in paragraph 7.1. First, it shows the important decision criteria for acquiring a new identification technology. Second, the performance of the µDtect compared to competitors is assessed. This chapter ends with the implications for the µDtect that came forth from the early economic evaluation (7.2).

7.1 Multiple criteria decision analysis

As the theory suggested, the MCDA consists of eight stages which guide a decision maker to choose between alternatives. In the case of the µDtect the goal is to find out what potential customers deem important and show how well the µDtect perform on those points compared to other available technologies. The comparison provides an indication on what aspects further development of the µDtect is required in order to improve the expected clinical and commercial value. The µDtect, and other technologies under consideration, are still in development and accurate data is not available for all alternatives and attributes.
The following paragraphs show the results of the MCDA performed for the µDtect case.

7.1.1 Decision context and alternatives

The decision context is distilled from the clinical case analysis (chapter 5). The possible markets identified here were laboratories in western countries, laboratories in developing countries, and remote areas. For the collection of data for this early economic evaluation there was access to experts working with and/or in Dutch microbiology laboratories. Therefore, the decision context for which this economic evaluation is applicable for the microbiology laboratory in the Netherlands and to some extent to laboratories in western countries.

In the clinical case analysis (chapter 5) four competitors were identified. Together with the µDtect brings this a total of five alternatives which will be evaluated in this section. The alternatives are:

- µDtect: The alternative under consideration for entering the medical market.
- MALDI-TOF/MS: This is the current state of the art, and therefore the main competitor for the µDtect for entering the market.
- Raman spectroscopy: Not yet widely implemented in the medical environment, but has promising features to which it can be(come) a competitor to the µDtect.
- Real time PCR: Technology which is in development for rapid identification with high accuracy of a broad range of microorganisms when a specific microorganism is targeted. Not integrated in the standard identification process in microbiology laboratories.
- Lab on a chip: A promising technology in development for rapid identification where only a small sample is needed without extensive cultivation. Further development is needed to become enter the market, but can become a competitor of the µDtect.

7.1.2 Identify relevant attributes and construct a value tree

The elicitation of relevant attributes is done by means of eleven face to face semi-structured interviews. The interviewees were asked which attributes were of importance for the decision of acquiring a new microbiology identification technology. After three interviews the attributes were identified and none were added in the later interviews. In each interview the respondents were asked if there were attributes missing. The first three interviews were with a head of the health care technology department, a microbiology physician, and a head of the microbiology laboratory unit. In total, 13 attributes were identified, which are part of three main categories; cost of ownership, clinical performance, and impact on workflow. The attributes together with a short description can be found in table 12. The value tree constructed from the attributes consists of three levels and can be found in figure 11.

Attributes	Description
Purchase costs	The amount of money to be paid to acquire the technology.
Implementation costs	The costs made to adjust the work environment and/or procedures in order to get the technology into working condition
Initial training costs	Costs of training personnel to learn to work with the technology
Maintenance costs	Costs of maintenance and repair of the technology
Cost of consumables	Costs of materials used when using the technology and performing an identification test
Training upkeep costs	Costs of training the personnel to sustain the required knowledge level to use the technology
Man hours used	The amount of labour time needed for performing a test
Accuracy	Percentage of correct identifications
Time to identification	The time it takes to identify a micro organism
Chance of contamination	The possibility of contaminating the blood sample in the process
Ease of use	The amount of hassle while using the technology
Integration with other systems	How well the technology can be combined with other procedures/machines. ICT coupling is an important determinant of this criterion.

Table 12: Description of the attributes

The value tree is judged by the criteria that are set up by Keeney & Raiffa [44]:

Completeness

The tree is checked for completeness. In ten interviews the interviewees are asked whether they found all the criteria present in the value tree.

Operationality

Operationality is about whether criteria in the lowest level are deemed specific enough for making a decision. The criteria “ease of use” gave some discussion on this point. What was meant by “ease of use” and how to measure it were questions raised on two occasions. “Number of failed tests due to human error” or “number of process steps” were suggested as more specific ways of describing for “ease of use”. Although, these are factors that influence and determine the “ease of use”, splitting the criterion to a lower level would make the value tree larger. A larger tree means more decisions to

be made and it did not add much for providing information about introducing the µDtect to the market. On basis of the judgment criteria of "minimum size" (see below) it has been decided to not split the criterion into lower level criteria.
"Integration with other systems" is a criterion which could be specified more. This can be done when is known with what other systems the integration should be, this will be laboratory or case specific. Because in this research an assessment is made for laboratories in the Netherlands it is not useful to specify this criterion into further detail.

Decomposability
Decomposability is about whether it is possible to assess the attractiveness of one option on one criterion independently of its attractiveness on other criteria.
It may be possible that the criteria Initial training costs and training upkeep cost can covariate with the ease of use. It may be so that the more hassle it is to operate a device (ease of use) the more training the employees require to operate the device. Although it may as well be that there are many process steps (lot of hassle), but which are all very easy and not much training is required for operating the device.

Absence of redundancy
There are no duplicating attributes in the value tree.

Minimum size
Decreasing the size would diminish the information value for what is deemed important for introducing a new identification technology. Increasing the tree could make some criteria easier to measure, but would not add much information about a possible introduction of the µDtect while it is in the development phase.

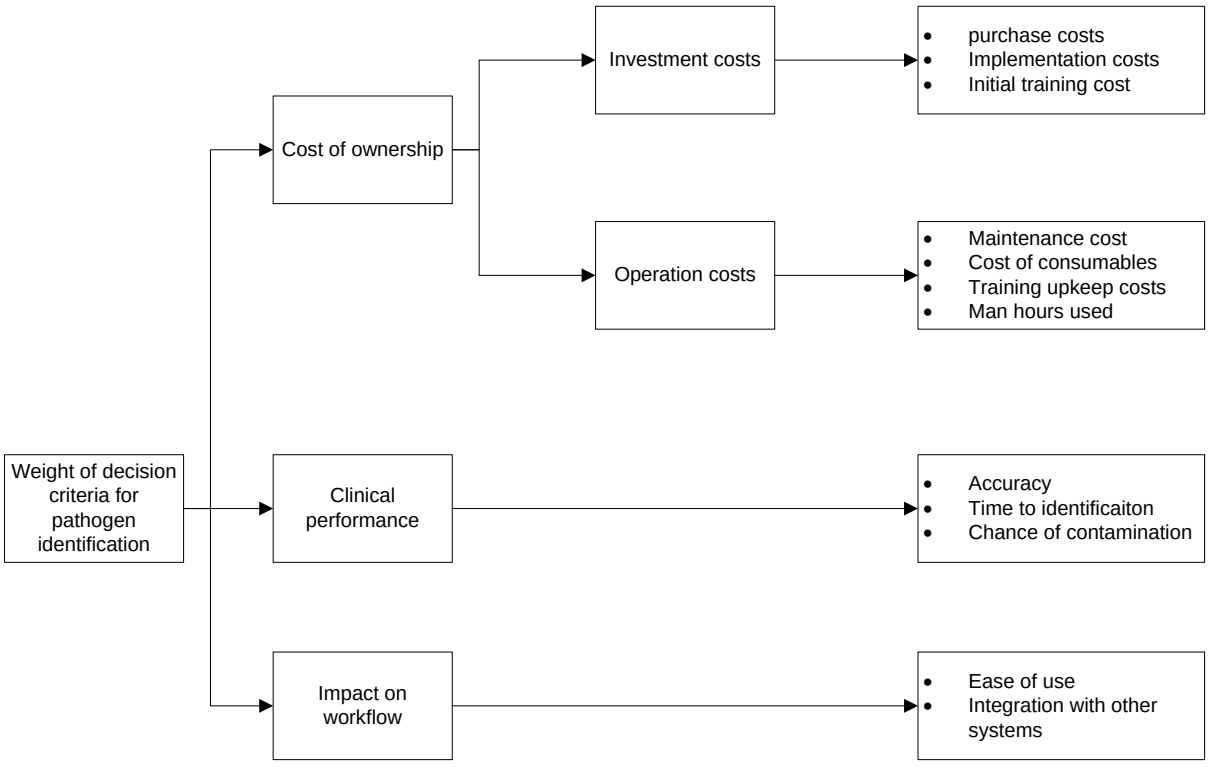


Figure 11: Value tree

7.1.3 Determination of weights

The determination of the relative importance of attributes is determined by the allocation of 100 points within a certain category at a certain level. For example: 100 points had to be allocated between “cost of ownership”, “Clinical performance”, and “impact on workflow”. 100 points had to be allocated between the attributes within the categories as well, for example between “accuracy”, Time to identification”, and “chance of contamination”. Therefore, in total 100 points had to be allocated six times. Four microbiology physicians and one unit head of the microbiology laboratory, one head of biomedical technology department, two clinical physicists, and one manager microbiology laboratory, were requested to allocate the points. One clinical physicist could not determine the preferences because it was too case dependent. His/Her preferences for acquiring a microorganism identification device were dependent on the situation. For example, in time of an epidemic the criterion “time to identification” would be deemed much more important than costs, than that it would be when there were no epidemic.

One microbiology physician was interviewed by phone and therefore not confronted with the value tree.

The value tree has been adapted based on the first few interviews. Therefore there are some missing preferences. One clinical physicist could not express his preferences for the criteria within the operation cost category. The preferences of the respondents are displayed in table 13, NA stands for not available and are missing values. The cases with the missing values are not omitted. The missing values are imputed based on the averages of the values given for the same criteria by other respondents. The calculation of the overall preferences are based on the available data of the attribute. For the calculation of the preferences of the microbiology physicians and the group supporting personnel, this is done based on the values within the group.

Respondent	1	2	3	4	5	7	8	9	11
Function	MP	MP	MP	MP	MP	UML	MML	HBT	CP
Cost of ownership	5	30	20	20	15	10	20	20	40
Clinical performance	80	50	50	60	60	60	40	50	50
Impact on workflow	15	20	30	20	25	30	40	30	10
Investment costs	50	40	50	20	40	30	30	40	50
Operation costs	50	60	50	80	60	70	70	60	50
Purchase costs	10	50	70	40	34	40	80	34	34
Implementation costs	70	30	20	20	33	30	10	33	33
Initial training costs	20	20	10	40	33	30	10	33	33
Maintenance costs	10	40	20	40	30	30	50	30	NA
Cost of consumables	80	40	40	20	5	30	30	20	NA
Training upkeep costs	10	20	10	10	15	40	10	30	NA
Man hours used	NA	NA	30	30	50	NA	10	20	NA
Accuracy	67	70	60	40	40	50	30	60	40
Time to identification	33	15	30	40	50	25	50	10	20
Chance of contamination	NA	15	10	20	10	25	20	30	40
Ease of use	50	67	40	60	60	50	60	30	70
Integration with other systems	50	33	60	40	40	50	40	70	30

Table 13: Attribute preferences of respondents. MP = Microbiology Phycisian, UML = Unit head microbiology laboratory, MML = Manager microbiology laboratory, HBT = Head biomedical technology, CP = Clinical physicist

Overall preferences

When looking at the overall preference it can be seen that the clinical performance of a microbiology identification device is perceived as the most important category (0,56), followed by the impact on workflow category (0,24) and the cost of ownership as the least important (0,20) (Figure 12). Within the cost of ownership, the operations costs are deemed more important (0,61) than the initial investment costs (0,39).

Of the individual decision criteria the accuracy is deemed most important (0,274), followed by time to identification (0,165), and ease of use (0,132). The initial training costs (0,02) and training upkeep costs (0,02) are perceived as the least important.

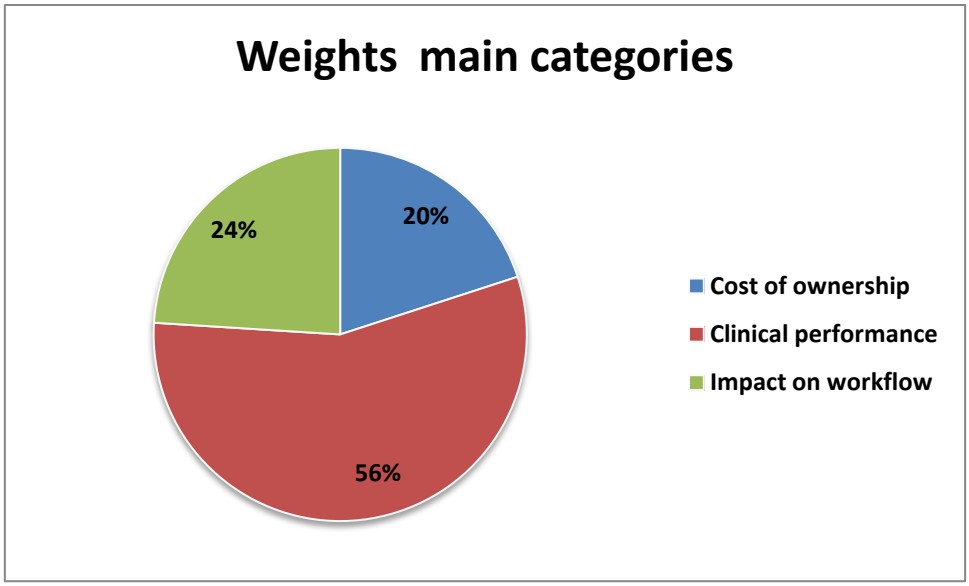


Figure 12: weights main categories

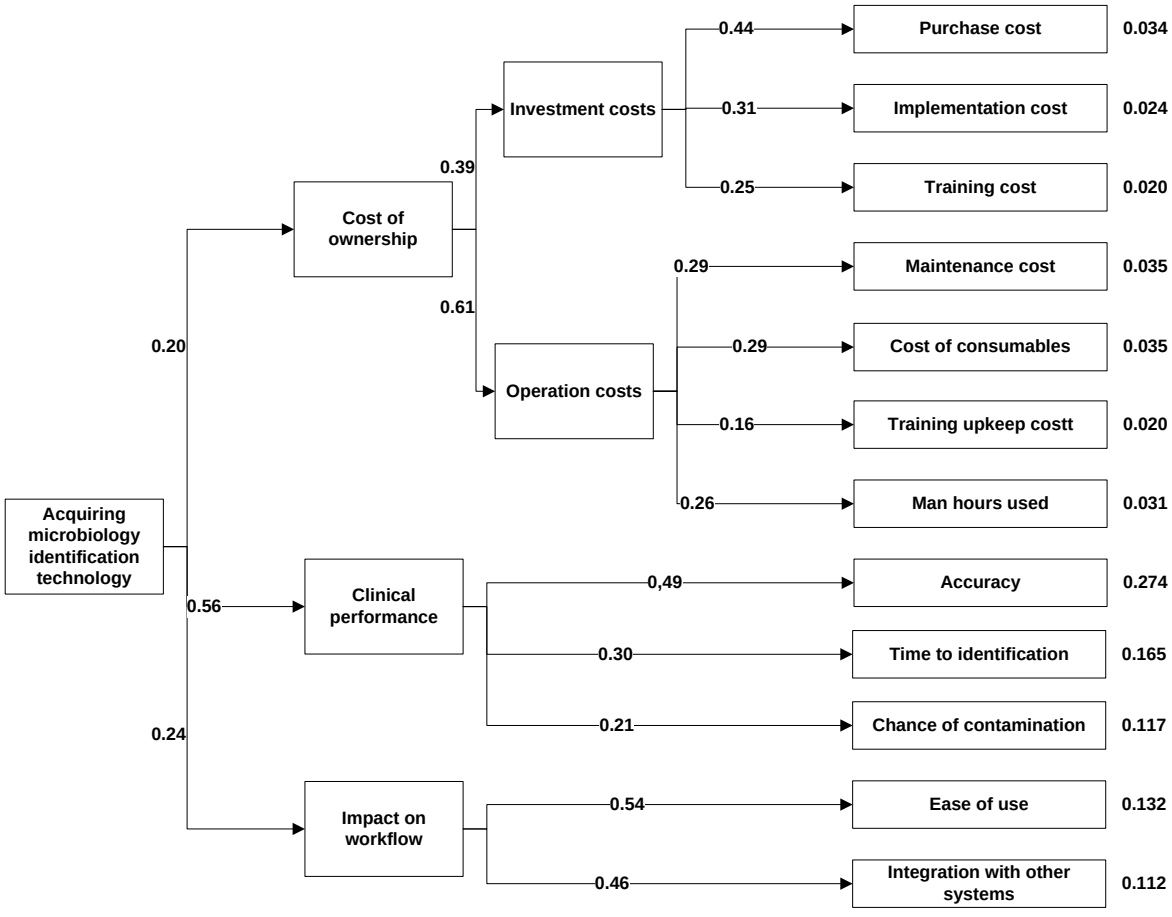


Figure 13: Overall preferences

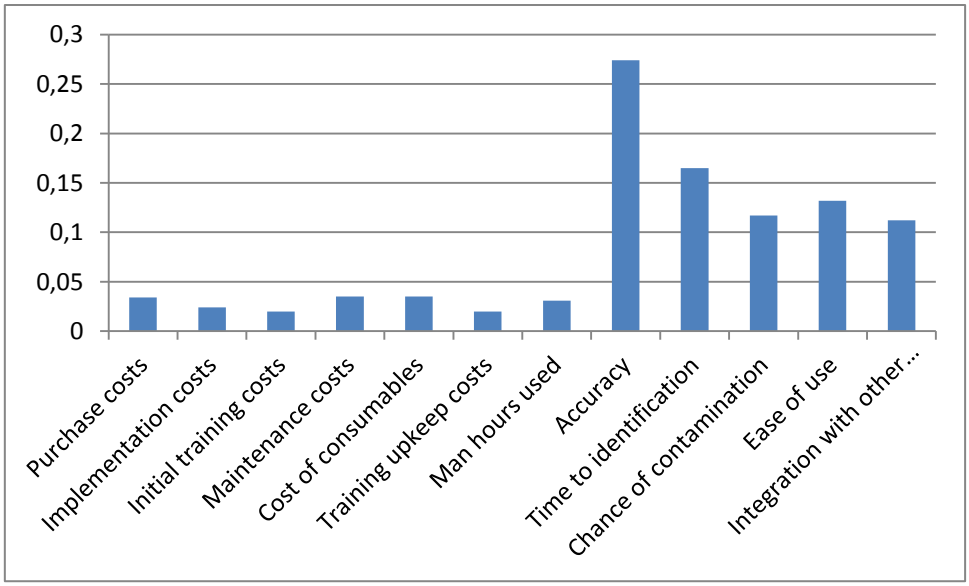


Figure 14: Overall weigths lower level attributes

Preferences microbiology physicians

The microbiology physicians deem the clinical performance of a clinical microbiology identification device as most important (0.60). Cost of ownership (0,18) and impact on workflow (0,22) are deemed of almost equal importance. Accuracy (0,322) is the most important attribute, followed by time to identification (0,197), and ease of use (0,122). Training upkeep cost (0,012) and training cost (0,018) are deemed the least attributes.

Preferences supporting personnel

Supporting personnel deem the clinical performance (0,50) of a clinical microbiology identification device the most important category as well, but to a less extent than the microbiology physicists. Impact on workflow (0,27) and the cost of ownership (0,23) are deemed significantly less important than clinical performance. Supporting personnel deem the accuracy (0,225) as most important attributes, followed by chance of contamination (0,144) and ease of use (0,144). Least important are the man hours used (0,020), the implementation cost (0,022) and the initial training cost (0,022).

Microbiology physician versus supporting personnel

The opinion of the importance of decision criteria according to the microbiology physicians and according to the supporting personnel differ. The differences are visualized in figure 15. The largest differences are between the criteria: Accuracy, time to identification, and chance of contamination which are all criteria from the clinical performance category.

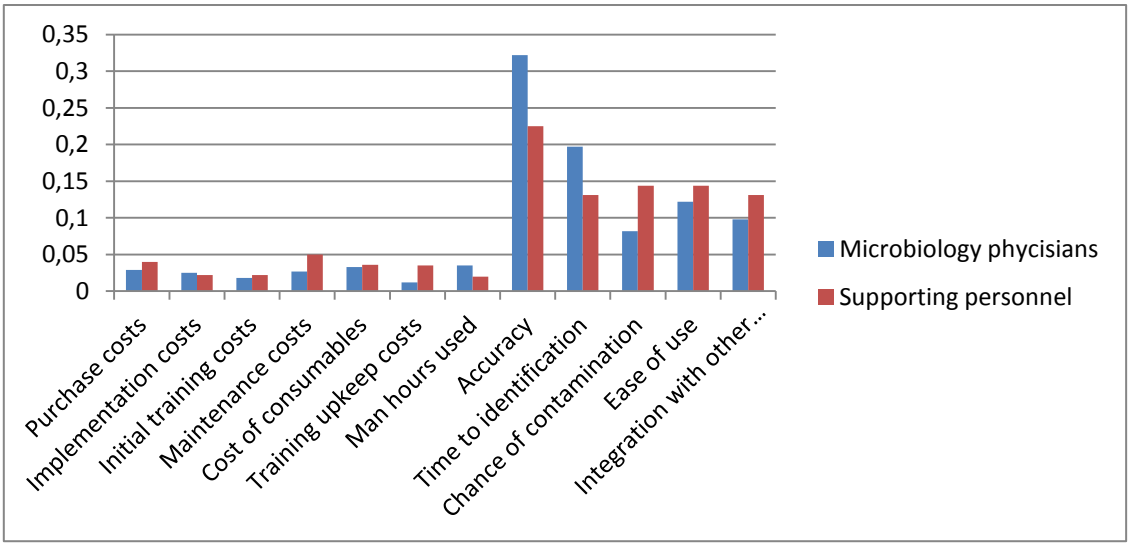


Figure 15: Preferences Microbiology physicians versus supporting personnel

7.1.4 Performance of the alternatives on the attributes

The results of the research at performance of the alternatives are presented in this paragraph. This starts with an operationalization of the attributes. The performance of the alternatives per attribute has been given with a short explanation and the source of the data. The performances have been compiled in a performance matrix followed by the point estimates on an interval scale.

The performances of the alternatives are determined in four ways. First, the scientific literature is searched for data. The alternatives and attributes in any combination have been used as search term within Google scholar. Only articles from 2000 or later were considered. When no scientific data was available, non scientific documentation were used. These documents were gathered from websites and provided by hospitals and/or companies. When no documentation was available expert opinions/estimations were used. When none of above was available an estimation has been made by the researcher.

Performance per attribute

Purchase costs

The initial purchase costs are measured in Euros (€) on a ratio scale. Prices can differ per provider. Intervals are used to take this variance into account.

Performance on attribute "purchase costs"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	€20.000	Purchase costs of €200, - for a device that can analyze 4 bottles is estimated. For a device that can analyze 400 bottles the costs are estimated on 20.000	Estimation by the eNose company
MALDI-TOF/MS	€120.000	Kliem states that the MALDI-TOF/MS costs about 120,000 USD or Euro.	[79-80]
Raman spectroscopy	Average: €46.000 Range: €40.000 - €52.000	There are many types of Raman spectroscopy devices.	[80-81]
Real time PCR	Average: €47.500 Range: €25.000 - €70.000	There is a wide range of real time PCR devices available.	[82]
Lab on a chip	Average: 35.000 Range: €25.000 - €45.000	The lab on a chip microbiology analysis devices now often are combined with real time PCR techniques. Therefore, the average price will be at least that of a real time PCR.	Estimation, [83-85]

Table 14

Implementation costs

The costs of implementing a device are very case specific. Therefore, it is not possible to express it in exact monetary terms. An ordinal scale (very low, low, mediocre, high, very high) is used for measuring this criteria. Underlying attributes for the determination of the implementation costs are: how large the device is, possible ICT requirements, and the requirement of adjusting the (work) environment.

Performance on attribute "implementation costs"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Low	Will be as large as the current Bactec™ incubation devices.	The eNose company
MALDI-TOF/MS	Low	Fits on a desktop.	Interview, observation
Raman spectroscopy	Low	Fits on a desktop.	[86]
Real time PCR	Low	Fits on a desktop.	[82]
Lab on a chip	Low	Fits on a desktop.	[85]

Table 15

Initial training costs

For technologies still in development it is only possible to give an indication. This indication is based on specific knowledge required, number of process steps, and expected difficulty level for operating the device, which all have influence on the time required to learn to be able to operate the device. Therefore, this criterion will be measured on an ordinal scale (very low, low, mediocre, high, very high).

Performance on attribute "initial training costs"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Very low	There is no preparation needed for the sample, the computer will indicate whether a microorganism is detected and/or identified.	Internal document eNose company
MALDI-TOF/MS	Low	The technical requirements can be learned by inexperienced personnel in less than 1 week training. Require some handling for sample preparation.	[87]
Raman spectroscopy	Low	Does not require much technical expertise to operate.	[88]
Real time PCR	High	The analysts need training in molecular methods. Knowledge about primers is required.	[8]
Lab on a chip	Low	Place the chip with the sample in the identification device.	Assumption

Table 16

Maintenance costs

Maintenance costs are device specific and supplier specific. Service and maintenance contracts are mostly agreed as part of the purchase. Estimations can be made based on the costs of the parts of the machine and the complexity of the machine.

Performance on attribute "maintenance costs"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Very low	The components of the µDtect are very low cost and can easily be replaced.	Internal documents eNose company
MALDI-TOF/MS	High	10% of the purchase price.	[89]
Raman spectroscopy	Medium	10% of the purchase price.	[89]
Real time PCR	Medium	10% of the purchase price.	[89]
Lab on a chip	Low	A significant part of the technology will be in the disposable chip. When this breaks, the chip can easily be replaced.	Estimation

Table 17

Cost of consumables

The cost of consumables is measured on a ratio scale in Euros (€). There is information available about the costs per test or expected costs per test.

Performance on attribute "cost of consumables"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	€0.60	The Odocap® will add €0.60 to each test.	Internal documents
MALDI-TOF/MS	€0.40	High confidence test cost about €0.40, for this test a cultivation is required. The MALDI-TOF/MS test directly after incubation cost around €8,50,- USD. This performance is based on the high confidence test because that is the standard used in clinical microbiology laboratories.	[69]
Raman spectroscopy	Average: €23,- Range: €11 - €35	Average assumed to be €23,-	[81]), Interviews
Real time PCR	Average: €4,51 Range: €1,48 - €8,30	The average is €4,51	[8]
Lab on a chip	Average: €20 Range: €10,- - €100,-	For routinely diagnosis in a clinical microbiology laboratory the cost of consumables will probably be closer to the €10,- than the €100,-.	[90]

Table 18

Training upkeep costs

Training upkeep costs depend on how much personnel needs to be trained when new knowledge becomes available. Costs can differ between technologies on this aspect, for example: when the technology develops and it is able to identify a new pathogen, does the analyst need to know a new procedure or will it just be added to a database and doesn't there change much for the analyst. The performance on the attribute "training upkeep costs" is expressed and measured on an ordinal scale (very low, low, medium, high, very high).

Performance on attribute "training upkeep cost"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Low	Database needs to be updated; technique stays the same when a new microorganism becomes identifiable.	Estimation by experts from the e-Nose company
MALDI-TOF/MS	Low	Database needs to be updated; technique stays the same when a new microorganism becomes identifiable.	Interview, [79]
Raman spectroscopy	Low	Database needs to be updated; technique stays the same when a new microorganism becomes identifiable.	[91]
Real time PCR	High	Development of protocols for new microorganisms require skill and a significant amount of time and recourses.	[8, 92],interviews
Lab on a chip	Medium	For a new type of microorganism the right chip needs to be selected. This requires some training.	Estimation

Table 19

Man hours used

Man hours used per test are expressed in minutes on a ratio scale.

Performance on attribute "man hours used"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Average: 1,5 minutes Range: 1-2 minutes	Place the flask in the device. No preparation needed.	Internal documents eNose company
MALDI-TOF/MS	Average: 7,5 minutes Range: 5 – 10 minutes	Preparation of sample from plates.	Interviews
Raman spectroscopy	Average: 22,5 minutes Range: 15 – 30 minutes	Based on sample preparation	[81, 91, 93]
Real time PCR	6 minutes	Based on the Taqman real time PCR	[92]
Lab on a chip	Average: 3 minutes Range: 2-4 minutes	Based on sample preparation	[93]

Table 20

Accuracy

The accuracy differs for each pathogen and each identification technology. Therefore, to be able to give an indication of accuracy of each alternative, the performance on the top 4 important pathogens as identified in the clinical case analysis (chapter 5) will be averaged. The pathogens as identified are: Staphylococcus Aureus, Streptococcus Pneumoniae, Eschericha Coli, and the Staphylococcus Epidermidis. The accuracy will be measured in percentage of correct identifications of the total tests.

Performance on attribute "accuracy"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Average 84% Range80 - 88	Based on a proof of principle study by Bruins (2009).	Internal documents, [10]
MALDI-TOF/MS	Average 97% Range 96 – 99%	Based on studies from Kovacevic (2011) and Knight (2011).	[94-95]
Raman spectroscopy	Average 98% Range97 – 99%	Based on the four important bacterial pathogens.	[96-97]
Real time PCR	Average 97% Range 95 – 98%	Based on the four important bacterial pathogens.	[93, 98]
Lab on a chip	Average 93% Range 90-95 %	There are no hard data available for the accuracy of the LoC. This performance is an estimation made by Heo et al (2009).	[99]

Table 21

Time to identification

Time to identification is expressed in hours on a ratio scale.

Performance on attribute "time to identification"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Average: 10 hours Range: 8 – 12 hours	Detection and identification during the incubation phase.	[10]
MALDI-TOF/MS	Average: 14 hours Range: 12 – 16 hours	8-12 hours incubation, 4 hours enrichment, several minutes analyzing.	Interviews
Raman spectroscopy	Average 14,5 hours Range: 12,5 - 16,5 hours	8-12 hours incubation, 4 hours enrichment, 20 minutes for preparation and analysis.	[91, 93]
Real time PCR	3,5 hours	Based on tests with the TaqMan real time PCR.	[92]
Lab on a chip	Average: 3,8 hours Range 3,5 -4,25 hours	Amplification of sample required.	[85, 93]

Table 22

Chance of contamination

Contamination of samples can have several causes. It can already be present in the sample originated from for example a needle or the skin, but can also happen during handling of the sample during the identification process. The contamination concerned here is caused by handling the sample for preparation of the identification, by exposure to air and by the usage of the identification device. Each process step and each handling increases the chance of contamination. It is hard to say with certainty that a contamination is caused by the handling for the identification, but the number of process steps give an indication.

Because it is hard to be precise, this criterion will be measured on an ordinal scale (very low, low, mediocre, high, very high).

Performance on attribute "chance of contamination"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Very low	The sample is not handled often because of that no sample preparation is needed. The sample is sealed by the Odotag®.	Internal documents
MALDI-TOF/MS	Low	Sample preparation requires some sample handling.	Assumption based on required sample handling
Raman spectroscopy	Low	Sample preparation requires some sample handling.	Assumption based on required sample handling
Real time PCR	Low	Chance of contamination is low due to sealed reactions	[82]
Lab on a chip	Medium	Clogging up is an issue as well as metering and transporting solution which can cause (cross) contamination between steps.	[99]

Table 23

Ease of use

Ease of use was measured on an ordinal scale (very easy, easy, moderate, hard, very hard). Attributes that give an indication of the ease of use are the number of process steps, and past experience of users.

Performance on attribute "ease of use"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Very Easy	No sample preparation. Input in the device very easy. Results easy to read/interpret.	Internal document e-Nose company
MALDI-TOF/MS	Easy	Require some sample preparation. Input in the device very easy. Results easy to read/interpret.	[67]
Raman spectroscopy	Moderate	Require some sample preparation. Input in the device very easy. Results interpretation of medium difficulty.	[91]
Real time PCR	Hard	Complex due to primer selection. Require some sample preparation. Input in the device very easy. Results easy to read/interpret.	[92-93]
Lab on a chip	Very easy	Sample preparation very simple. Input in the device very easy. Results easy to read/interpret.	Estimation based on description of use

Table 24

Possibility of integration with other systems

To determine the level of possible integration with other systems the alternatives will be judged upon whether it can: be linked with ICT for information sharing, easily fit in the current clinical set-up, and possible degree for automation. This will result in an ordinal scale (very low, low, mediocre, high, very high).

Performance on attribute "possibility of integration with other systems"			
Alternative	**Performance**	**Explanation**	**Source**
µDtect	Easy	Device fits in the current process steps. No sample loss.	Internal documents
MALDI-TOF/MS	Easy	Easily digitalized	[79]
Raman spectroscopy	Easy	No sample loss.	Estimation based the wide applicability and no sample loss
Real time PCR	Easy	High potential for automation. No sample loss.	[92]
Lab on a chip	Mediocre	Potential for automation. Sample loss.	[77, 84]

Table 25

Point estimates on an interval scale

The performances of the attributes are translated to point estimates. The point estimates are calculated on an interval scale ranging from 0 – 100. This calculation is done based on a linear function.

Inverse functions are used where needed. For example "purchase costs": the lower the purchase price the better. Therefore, the µDtect with a performance of €20.000 gets a point estimate of 100, and the MALDI-TOF/MS with a performance of €120.000 a point estimate of 0 points.

For the point estimates in table X the average performances are used.

	µDtect	MALDI-TOF/MS	Raman spectroscopy	Real time PCR	Lab on a chip
Purchase costs	100	0	74	73	85
Implementation costs	100	100	100	100	100
Initial training costs	100	75	75	0	75
Maintenance costs	100	0	33	33	67
Cost of consumables	99	100	0	82	13
Training upkeep costs	100	100	100	0	50
Man hours used	100	71	0	79	93
Accuracy	0	100	100	93	57
Time to identification	41	5	0	100	95
Chance of contamination	100	50	50	50	0
Ease of use	100	66	33	0	100
Integration with other systems	100	100	100	100	0

Table 26

7.1.5 Utility scores

By multiplying the performance on an attribute with the weight of the attribute and add these all up for each alternative results in a utility score for the alternatives. This utility score gives an indication of the weighted performance of the alternatives.

Table X shows the utility scores based on the average performance. The real time PCR (70,4) shows the highest utility score, the µDtect (62,7) is listed third. The µDtect scores high on the attributes in the "cost of ownership" category and the "impact on workflow" category. On the attributes within the "clinical performance" category, and especially the accuracy, the µDtect performs less compared to the other alternatives. The "clinical performance" attributes have a high weight, and therefore have a large impact on the utility score.

The MALDI-TOF/MS (65,6), which is currently the state of the art, has the second highest utility score and the Raman spectroscopy (58,4) the fourth. The LoC (58,0) technology has the lowest utility score. A reason for this could be that the technology is still in a development phase and a lot of aspects require further development.

The utility scores of the Raman spectroscopy and the Lab on a chip technology lie relatively close, as are the scores of the µDtect and the MALDI-TOF/MS.

	µDtect	MALDI-TOF/MS	Raman spectroscopy	Real time PCR	Lab on a chip		Weight decision criteria
Purchase costs	100	0	74	73	85		0,034
Implementation costs	100	100	100	100	100		0,024
Initial training costs	100	75	75	0	75		0,02
Maintenance costs	100	0	33	33	67		0,035
Cost of consumables	99	100	0	82	13		0,035
Training upkeep costs	100	100	100	0	50		0,02
Man hours used	100	71	0	79	93		0,031
Accuracy	0	100	100	93	57		0,274
Time to identification	41	5	0	100	95		0,165
Chance of contamination	100	50	50	50	0		0,117
Ease of use	100	66	33	0	100		0,132
Integration with other systems	100	100	100	100	0		0,112
Utility score	**62,7**	**65,6**	**58,4**	**70,4**	**58,0**		

Table 27

7.1.6 Sensitivity analysis

A sensitivity analysis by means of scenarios has been performed in order to check the robustness of the analysis. The scenarios used are the “worst case scenario”, “best case scenario”, and the “High accuracy scenario”. In the worst case scenario the lower bounds of the performance of the µDtect are used and the upper bound of the competing alternatives. In the best case scenario the upper bounds of the performance of the µDtect are used and the lower bounds of the performances of the competing alternatives. In the high accuracy scenario it has been assumed that through research and development the accuracy of the µDtect is high.

Worst case scenario

In the worst case scenario the utility score of the µDtect (56,9) is the lowest compared to the other alternatives, the real time PCR still has the highest utility score (71,7). The LoC technology (65,2) went from fifth place to the third. The MALDI-TOF/MS (65,9) remained second and the Raman spectroscopy (58,6) fourth.

Worst case scenario							
	µDtect	**MALDI-TOF/MS**	**Raman spectroscopy**	**Real time PCR**	**Lab on a chip**		**Weights**
Purchase costs	100	0	80	95	95		0,034
Implementation costs	100	100	100	100	100		0,024
Initial training costs	100	75	75	0	75		0,02
Maintenance costs	100	0	33	33	67		0,035
Cost of consumables	98	100	0	90	9		0,035
Training upkeep costs	100	100	100	0	50		0,02
Man hours used	100	77	0	69	100		0,031
Accuracy	0	100	100	95	79		0,274
Time to identification	6	6	0	100	100		0,165
Chance of contamination	100	50	50	50	0		0,117
Ease of use	100	66	33	0	100		0,132
Integration with other systems	100	100	100	100	0		0,112
Utility score	**56,9**	**65,9**	**58,6**	**71,7**	**65,2**		

Table 28: Worst case scenario analysis

Best case scenario

The results of the best case scenario are presented in table X. In the best case scenario the µDtect (73,6) has the highest utility score followed by the real time PRC (67,3). The MALDI-TOF/MS (63,2) ranks third and the Raman spectroscopy (60,4) fourth. The LoC's (41,3) utility score dropped due to that it has the worst performance on the accuracy attribute in this scenario.

Best case scenario							
	µDtect	**MALDI-TOF/MS**	**Raman spectroscopy**	**Real time PCR**	**Lab on a chip**		**Weights**
Purchase costs	100	0	68	50	75		0,034
Implementation costs	100	100	100	100	100		0,024
Initial training costs	100	75	75	0	75		0,02
Maintenance costs	100	0	33	33	67		0,035
Cost of consumables	100	100	65	91	0		0,035
Training upkeep costs	100	100	100	0	50		0,02
Man hours used	100	69	0	83	90		0,031
Accuracy	25	92	100	83	0		0,274
Time to identification	65	4	0	100	94		0,165
Chance of contamination	100	50	50	50	0		0,117
Ease of use	100	66	33	0	100		0,132
Integration with other systems	100	100	100	100	0		0,112
Utility score	**73,6**	**63,2**	**60,4**	**67,3**	**41,3**		

Table 29: Best case scenario analysis

High accuracy scenario

The results of the high accuracy scenario are presented in table X. The assumption that the µDtect has a high accuracy has a significant effect on its utility score (90,1) and is ranked first. The real time PCR (68,9) is in second place.

This scenario shows the impact of the accuracy attribute. Change of the performance on this attribute can swing an alternative from least preferred to most preferred.

	µDtect	MALDI-TOF/MS	Raman spectroscopy	Real time PCR	Lab on a chip		Weights
Purchase costs	100	0	74	73	85		0,034
Implementation costs	100	100	100	100	100		0,024
Initial training costs	100	75	75	0	75		0,02
Maintenance costs	100	0	33	33	67		0,035
Cost of consumables	99	100	0	82	13		0,035
Training upkeep costs	100	100	100	0	50		0,02
Man hours used	100	71	0	79	93		0,031
Accuracy	100	100	100	87,5	0		0,274
Time to identification	41	5	0	100	95		0,165
Chance of contamination	100	50	50	50	0		0,117
Ease of use	100	66	33	0	100		0,132
Integration with other systems	100	100	100	100	0		0,112
Utility score	**90,1**	**65,6**	**58,4**	**68,9**	**42,3**		

Table 30: High accuracy scenario analysis

Conclusion sensitivity analysis

The results from the sensitivity analysis gave an overview of the best and worst case and high accuracy scenarios. The results indicated that the ranking of the alternatives were sensitive to the chosen parameter intervals. This was especially the case for the ranking of the µDtect and the LoC alternative. The reason for this is that these alternatives are still in development. The interval ranges are wider than the ranges of the alternatives which are already on the market because there is more uncertainty about (the performance on the aspects of) the device.

7.2 Implications for the µDtect

The performance of the µDtect on the criteria in the “cost of ownership” and “impact on workflow” is promising. The µDtect performs better in these categories than the alternatives. The relative low costs and the fit within the workflow are the strong points of the µDtect. During further development these aspects should be maintained. The low costs provide opportunities for markets where less funds are available and therefore of greater importance.

In the category “clinical performance” the µDtect has a lower expected performance on accuracy and time to identification compared to the alternatives. And these decision criteria are deemed most important by the microbiology physicians, who are the potential future users, and the supporting personnel, who have influence on the acquiring of medical technology process. In the best case

scenario in the current state of development, the µDtect scores fourth on the accuracy criterion. In the worst case scenario and the analysis where the average scores are used the µDtect performance is the lowest of the alternatives. Would the µDtect be able to identify microorganisms with high accuracy, as the “high accuracy” scenario shows, then it has great potential for the clinical microbiology laboratory. Therefore, a point of focus for the development of the µDtect would be the increase of accuracy.

8.0 Forces of entry analysis

Forces of entry can have a significant influence on the success of introducing a new product to the market. They can become market introduction barriers for a product, although when managed, they may be turned into strengths. It is important that they are acknowledged and managed when developing and introducing a new product [15]. The goal of this part of the analysis is to identify the possible forces of entry which may affect an introduction of the µDtect to the clinical market. Therefore give answer to the following sub-question of this research:

What are the forces of entry and how do these affect a possible introduction of the µDtect?

First, the results of the identification of the forces of entry are described and categorized by use of content analysis (8.1).The implications of the potential forces of entry for the µDtect are presented in paragraph 8.2.

8.1 Forces of entry identification

For the identification of the forces of entry semi-structured interviews are held. Eleven people from seven peripheral hospitals, one independent laboratory, and a microorganism identification technology producer, were interviewed. By means of open ended questions the data was gathered for the identification. The group of respondents consisted of six microbiology physicians, one head of the microbiology laboratory unit, one microbiology laboratory manager, one head of medical technology, and two clinical physicists.

The interviews were written out based on audio recordings. Thematic coding is used to distill the possible forces of entry. Coding the interviews for the themes: introduction barriers, forces of entry, clinical or technical requirements, resulted in 37 meaning units. Content analysis is used for analyzing and categorizing the findings. Through interpretation the meaning units were labeled and 22 codes were identified. These codes are ordered into 10 sub-categories, which fall under 5 main categories (Table 31). These main categories are based on the forces of innovation in the health care market, as identified by Herzlinger [15].

Players

Internal politics in hospitals

During the process of acquiring new medical technology in hospitals several stakeholders are involved (see chapter 6). A request for acquiring a technology has to be made and an investment advisory committee evaluates these requests. This committee receives requests from all departments of the hospital, therefore a request have to compete with requests from other departments. The persons in the investment advisory committee are employees in the hospital and work in a department themselves. This can result in a conflict of interest. Personal relations between colleagues can have an influence on the advice as well. One microbiology physician and one clinical physicist mentioned that internal politics in a hospital is a force of entry for a new technology.

Existing contacts and contracts

The providers of the microorganism identification device currently equipped in the microbiologic laboratory already have a relationship. When the decision has to be made to replace the current device the current provider has a head start because they are already known. One microbiology physician and one laboratory manager identified that existing contracts and contacts can be an introduction barrier for a new technology. In practice, once chosen for a certain provider the

contract will just be renewed when replacement is needed. Only when a revolutionary new technology enters the market all providers are considered again.

Funding

Availability of funds

The amount of money available for investing in new medical technology is limited. Three respondents; two clinical physicists, and one laboratory manager identified this as a force of entry.
Funding becomes available when medical equipment is economically written off. The result of this system is that there is not much funds available for innovation. It is possible to get funds available sooner. When the business case clearly shows that the new device will return the investment in a relatively short period of time (3-5 years).

Reimbursement

The theory suggests that reimbursement can be an introduction barrier for new technologies [15]. In the Netherlands the reimbursement is incorporated in diagnosis related groups (DRGs) for which prices are set. The insurance company has to reimburse the set price to the healthcare provider. The costs made for the microbiologic identification is a small portion of this price. When a new identification technology increases or decreases the costs of the diagnosis, then this will not directly affect the reimbursement price. The extra costs, or savings, will be for the hospital or laboratory. Therefore, in the Netherlands reimbursement will not be a barrier of entry, in other countries this may be different.

Policy

Certificates

In order to be allowed to sell a medical technology a CE mark needs to be acquired. This mark indicates that the medical device complies with the European standards for safety and quality. For the distribution of a diagnostic device like the µDtect it has to comply with the Directive 98/79/EC on in vitro diagnostic medical devices. When it does it receives an In Vitro Diagnostic CE mark which is required to enter the European market.
For most countries a similar certificate is required in order to enter the market.

Introduction process in hospitals

Five interviewees identified the introduction process in hospitals as a potential barrier. Two clinical physicists, one laboratory manager, one microbiology physician, and one head of the department of medical technology. The main reason for the introduction process to become a possible barrier is that all departments within the hospital are competing for the same investment money. The added value and the necessity of the investment is compared to all the investment requests in the hospital. This approval for investment takes place once or twice a year in most hospitals. When an investment request is denied the request can be submitted for the next year.

Technology

Competitors

Eight interviewees identified competitors and future competitors as an introduction barrier for the µDtect. Six were microbiology physicians, one R&D director, one head of the laboratory unit, and one laboratory manager. The MALDI-TOF/MS was mentioned five times as the main competitor. The real time PCR is named twice as the most promising future competitor. It has the potential to identify directly from the blood sample, which would avoid the cultivation step altogether. Lab on a chip is mentioned once as a possible competitor.

Time reduction

The time to identification can be a introduction barrier as well as an opportunity. To turn it into an opportunity the time to identification of the µDtect should be significantly shorter compared to the

MALDI-TOF/MS. Significantly shorter would be more than 6 hours. When the time reduction would only be a few hours it will not be worth it to acquire a total new device. This force of entry is identified by six respondents; 5 microbiology physicians and one head of the bacteriology department.

Broad application
The µDtect is now developed for diagnosing blood samples. Three respondents, all microbiology physicians, identified that it could be a barrier of introduction when the µDtect can only diagnose blood samples. Samples of other body fluids and feces are diagnosed as well in microbiologic and immunologic laboratories. Several competing technologies are able to identify microorganisms in these samples. This can be a critical disadvantage for the µDtect.

Accountability
Proof of principle
One microbiology physician indicated that the proof of principle (Bruins et al., 2009) is performed with spiked samples. The concentrations of bacteria did not represent a situation in practice. In practice there can be as few as 1 bacteria per 10 ml., the tests are done with 10^8 bacteria per µl.
Clinical trials with patient materials need to be performed, otherwise this will become a barrier.

Proof of accurate identification for a broad range of microorganisms
Four interviewees, all microbiology physicians, said that the µDtect should be able to identify a broad range of microorganisms accurately. Staphylococcus Aureus, Staphylococcus Epidermidis, Pseudomonas, and Estrechia Coli are critical pathogens. Not being able to identify these accurately can result in that this force turns into a barrier. According to the respondents an accuracy of 95% or higher is required.

Theme	Forces of entry for the µDtect									
Category	**Players**		**Funding**	**Policy**		**Technology**			**Accountability**	
Sub-category	*Internal politics*	*Existing contacts and contracts*	*Availability of funds*	*Certificates*	*Introduction process in hospitals*	*Competitors*	*Time reduction*	*Broad application*	*Proof of principle*	*Identification for a broader range of microorganisms*
Codes	- Many departments with long communication lines	- Often prolonging existing contracts	- Funding becomes available when old machines are written off	- CE mark	- Competing with other departments in hospital	- MALDI-TOF/MS, cheap and no consumables	- At least 12 hours time reduction	- Applicability needs to be broader than just blood samples	- Done with spiked samples, not yet with patient samples	- Need to be able to identify broad spectrum of pathogens with accuracy
	- Internal politics can influence advisory committee	- Previous contracters preferred unless the technique is not really revolutionary	- Concurrentie other departments			- PCR, can be faster and more accurate in future	- Bactec + MALDI-TOF/MS can be just as fast	- MALDI-TOF/MS can identify braod scala of microorganisms		- Need to approach 100% accuracy for Staphylococcus Aureus, Pseudomonas, E. Coli, Candida (gist))
						- Lab on a chip, very fast directly from blood	- Time reduction too small for acquiring new device			- Need to be able to handle Polyflora with a minimum of 95% accuracy
						- Fully automated systems				
						- Directly from bloodsample without cultivation				

Table 31: Forces of entry identified by means of thematic coding

8.2 Implications for the µDtect

As Herzinger [15]stated, each of the forces of innovation can become an obstacle, but an opportunity as well. In this part the forces of entry will be discussed on how they will affect an introduction of the µDtect to the market. This assessment is done by answering the following questions for each possible barrier:

- How can these forces of entry be handled in order to avoid them from becoming introduction barriers, and potentially turn them into strengths?
- What are the potential consequences when the force of entry is ignored?

Internal politics

There will not be direct consequences for the introduction of the µDtect when internal politics are ignored. For an external medical technology producer there is not much that can be done about the internal politics in a hospital or laboratory. It can work in favour or against an introduction of the new technology. Providing clear information about the performance of the technology which makes a strong business case is a way to influence this force to some extent.

Existing contacts and contracts

Existing contracts can prevent an introduction of a new technology. Knowing when a contract is going to expire can help with focusing the marketing activities of the e-Nose company. The e-Nose company cannot prevent contact between possible customers and competitors. A way of influencing this force of entry is keeping the potential customers up to date about the developments around the µDtect.

Ignoring the contracts and the contacts between possible customers and competitors does not directly have an impact. Have knowledge about them could give e-Nose company a competitive edge though.

Availability of funds

The e-nose company does not have direct influence on when funds becomes available to invest in acquiring new identification technology. The force can be influenced to some extend by knowing when money becomes available. Time and resources for promoting the µDtect can be focused to the institutions where money is or will soon become available. Another way, which could avoid this potential obstacle altogether, is to make the µDtect so cost efficient compared to the competitors that it will earn itself back in a few years time.

This force of entry can be ignored without direct harm for the introduction of the µDtect, but by doing so there is a chance that time and resources are not used as effective as they could be, due to focusing on the wrong potential customer.

Reimbursement

In the Netherlands reimbursement is not a potential barrier for the introduction of the µDtect. In other countries it can be an introduction barrier and should be taken into account. For example: where people have to pay the health care costs out of pocket. Being able to diagnose blood samples at a lower cost than the method used can turn this force into a strength.

Certificates

Certificates are a prerequisite for entering the market with a medical technology. Without it an introduction is not possible. Therefore, ignoring it is not an option. Only legislators can remove the barriers that are the result of current laws and regulations. The eNose company does not have influence on it and has to comply to the regulations in order to overcome this barrier.

Introduction process in hospitals

A vendor company has very limited influence at the introduction process steps of hospitals and laboratories. Although, knowledge of the process can give insight in how to act and who to approach. Ignoring this barrier and thus not having knowledge about the process can seriously hinder an introduction of the µDtect.

The process of acquiring new medical technology in hospitals starts with the clinical expert, in the case of the µDtect with the microbiology physician. Convincing this stakeholder that the µDtect is an added value is essential. The departments within hospitals have to compete for the same investment budget. To increase the chances that the microbiology laboratory gets a part of the budget for investing in the µDtect, clear and compelling evidence should be provided about the added value of the µDtect.

Competitors

Competing technologies cannot be ignored. It is essential to know what the strengths and weaknesses are of the competing technologies in order to be able to position the µDtect onto the market. By focusing on the weak points of competitors and make those points the strong points of the µDtect this force can be turned into a strength. Another way is to focus on a (niche) market where the competition is slim. For the µDtect this could mean, focusing on identification of pathogens that are hard to detect with the current techniques. Another possibility is to search and focus on markets or countries where competitors have not entered the market yet. Developing countries may be an example of such market.

Time reduction

A significant time to identification reduction is essential when you want the µDtect to be the main identification device within a microbiology laboratory in the Netherlands. In that case, this clinical requirement cannot be ignored. The detection with the µDtect should be 6 – 12 hours faster than a direct MALDI-TOF/MS test.

Potential ways to reduce this barrier are to focus on the identification of microorganisms which are highly virulent. A fast identification can help to prevent spreading of the disease. A faster time to identification for highly virulent microorganisms is of greater value, and a minor time gain can be of importance.

Broad application

When you want the µDtect to be the main identification device within a microbiology laboratory this force of entry cannot be ignored. When the µDtect will not be able to identify other samples than blood samples, the chances of replacing for example the MALDI-TOF/MS will be slim. Further research and development is required in order to be able to achieve this.

This potential barrier can be avoided by focusing on the identification microorganisms that are difficult to detect with the current practice. In other words, focus on a niche market. This can have an impact on the amount of tests conducted with the µDtect.

Proof of principle

Proving that the electronic nose technology works for the identification of pathogens is a prerequisite for the introduction of the µDtect. Proof of that the µDtect can identify pathogenic bacteria within patient samples need to be delivered.

Proof of accurate identification for a broader range of microorganisms

When the µDtect will not be able to identify a broad range of microorganisms with high accuracy, the chances of replacing for example the MALDI-TOF/MS will be slim.

Further research and development can influence this force and to avoid that it will be a barrier. Another way to avoid is by focusing on the identification of specific, currently hard to identify, microorganisms. Being able to identify such microorganisms with high accuracy could position the µDtect into a niche market.

8.2.1 Conclusion

For the introduction of the µDtect the forces of entry have to be taken into account. Development decisions have to be made about to influence them.

From the analysis three critical forces are identified: certificates, competitors, and proof of principle. These forces cannot be ignored. When they are ignored, the chance of an introduction to the health care market will be near to nonexistent.

Two forces, the introduction process in the hospital and the possible time reduction, have a high priority. Knowing who and how to convince is the start of selling a new product. Time reduction has a high priority because it is potentially one of the strong points of the µDtect. If it is not possible to reduce the identification time significantly compared to that of a direct MALDI-TOF/MS, the chances of an introduction of the µDtect will decrease significantly for the Dutch clinical market.

Contracts and contacts, broad application, and identification of a broad range of pathogens, are of a medium priority. Strategic choices have to be made in order to avoid that these forces become barriers.

Forces of entry of the lowest priority are the internal politics and the available funds that institutions have for acquiring the medical technology. The e-Nose company does not have much influence on these forces. Ignoring them could hinder an introduction, but will not have serious consequences.

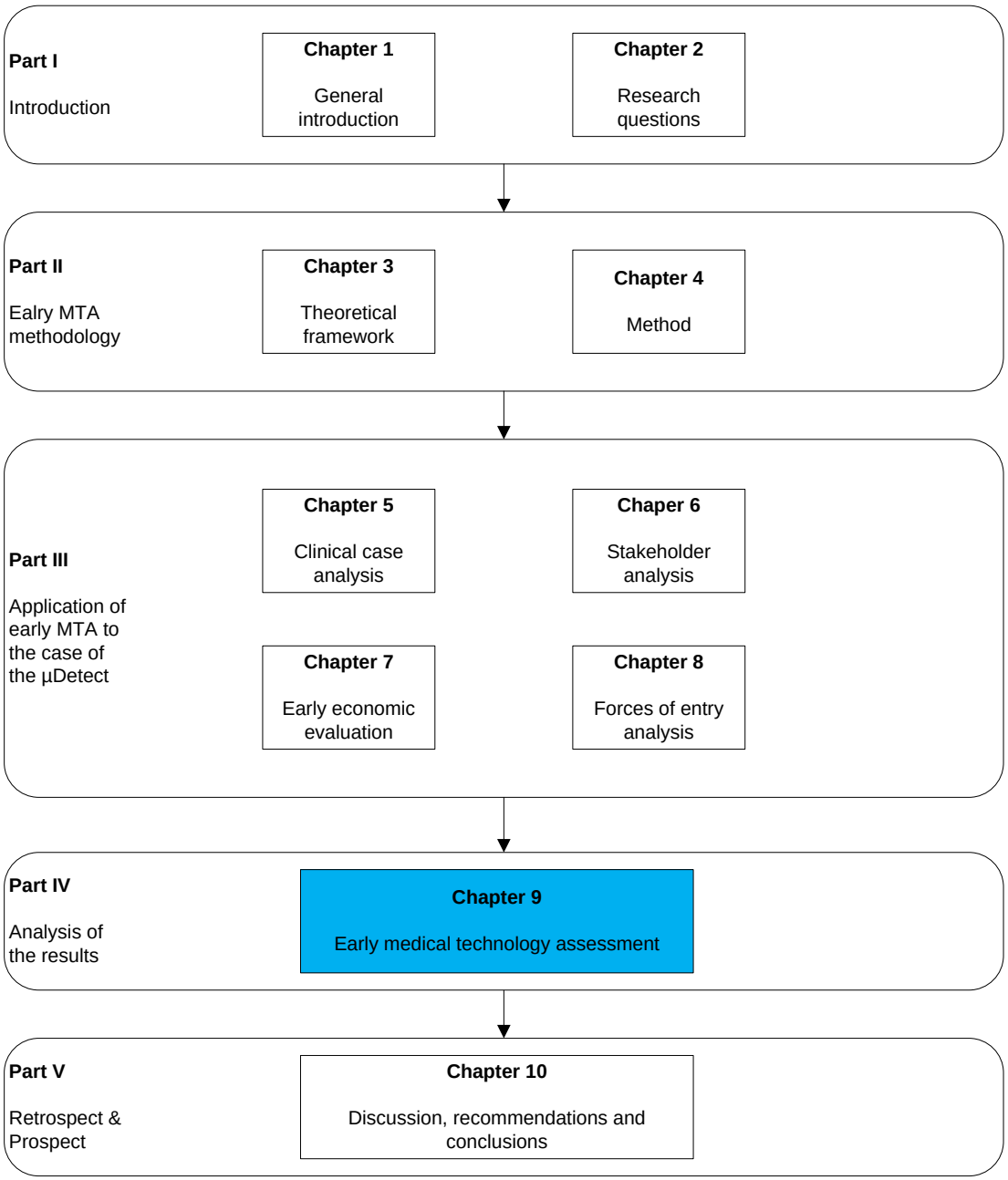
The eNose company should focus his attention on the critical and high priority forces of entry. Decisions have to be made to avoid that they will become introduction barriers and potentially turn them into strengths. A good strategy can improve the chances on a possible introduction significantly. Ignoring the low priority barriers will not have a real impact and should get the least attention of these possible barriers.

Possible barrier	Priority	Possible action
Internal politics	Low	Providing clear information
Contracts and contacts	Medium	Keep possible customers up to date about developments
availability funds	Low	Keep track when fund become available Increase cost-efficiency µDtect
Certificate	Critical	Comply with the regulations
Introduction process hospital	High	Know who to approach/convince Provide clear information
Competitors	Critical	Focus on weak points of competitors Focus at a niche market
Time reduction	High	Research and development Focus at specific pathogens
Broad application	Medium	Research and development Focus at specific pathogens
Proof of principle	Critical	Clinical trials
Identification of a broad range of pathogens	Medium	Research and development Focus at specific pathogens

Table 32: Priorities of the forces of entry

Part IV

Analysis of the results



9.0 Early medical technology assessment

This chapter presents the qualitative data synthesis of the information provided by the four analyses. Based on this information the main research question will be answered. In the first paragraph the important results of the analysis parts are presented (9.1). Through synthesis this data will be structured, which will provide the information that is the basis for answering the main research question (9.2).

9.1 Data from the analyses

Clinical case analysis

In the clinical case analysis the potential places of where the µDtect could be situated in the clinical pathway are identified. The results show that the µDtect should be placed in a clinical microbiology laboratory. There is less potential in application at the point of care, the general practitioner or the intensive care. The main reasons for this are that the expertise is not available at the point of care and susceptibility tests need to be done after identification and therefore the sample need to go to the laboratory anyway.

Every clinical microbiology laboratory is a potential place for the application of the µDtect. This can be in Western countries, developing countries, or at remote areas in for example a field hospital. The poorest countries are probably not a suitable market, because identification of the separate bacterial pathogens gives too detailed information which could not be acted upon. In these countries diagnoses are made based on symptoms, and treated with antibiotics that target a broad range of pathogens.

In the clinical case analysis the most important bacterial pathogens for the Western market are identified which a microbiology identification device should be able to identify with a high accuracy (95 – 98%). These are the Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, and the Eschericha Coli. These bacterial pathogens are important because they are most frequent. The Staphylococcus Aureus is important because it is highly virulent.

Stakeholder analysis

The results of the stakeholder analysis show the persons who have influence on the implementation and usage of the µDtect if it was introduced to the Dutch market. Key stakeholders are identified based on whether they have the urgency, legitimacy, and power to influence a decision. Stakeholders with all three attributes have the most salience and are the definitive stakeholders.

For acquiring a new microbiology identification technology in a hospital, the microbiology physician, the laboratory manager, the head of the department, and the hospital management, are the definitive stakeholders. For an external medical technology provider, the microbiology physician and the laboratory manager are the best approachable.

For the usage of the µDtect, after it would have been acquired, the microbiology physician and the analyst are definitive stakeholders.

Early economic evaluation

The early economic evaluation gave insight into two important aspects: what is deemed important in a microbiology identification device and how well does the µDtect perform compared to the competitors.

There are three categories of decision criteria distinguished: Cost of ownership, clinical performance, and impact on workflow. The results show that the clinical performance is deemed the most important (0,56) category, compared to the cost of ownership (0,20), and the impact on workflow (0,24). Within the category cost of ownership, the operation costs (0,61) are deemed more important than the investment costs (0,39).
On the level of the individual decision criteria the accuracy of the identification device is deemed the most important decision criteria (0,274), followed by the time to identification (0,165) and the ease of use (0,132).

The comparison done in the early economic analysis between the µDtect and the competitors show that the µDtect scores high in the categories "cost of ownership" and "impact on workflow". Except on the criteria "cost of consumables" the µDtect performs best on the individual criteria. The data show that the strong points of the µDtect are; that it is less expensive to operate and acquire than its competitors and that it is easy to fit in the current clinical procedures.
In the category "clinical performance", the performance of the µDtect is low compared to the competitors on the decision criteria "accuracy". It has the worst performance on this criterion of all the alternatives. On the criterion "time to identification" the µDtect scores average. On the criterion "chance of contamination" the performance of the µDtect is outstanding, because identification with the µDtect requires no additional sample handling for identification. Within the "clinical performance" category the accuracy is the main weak point of the µDtect.

Forces of entry analysis
The forces of entry analysis resulted in a list of possible barriers which can be or become opportunities as well. Each of the forces requires attention, because when ignored they can become barriers of entry, which would obstruct a market entry of the µDtect. During the forces of entry analysis there is a ranking made of which force has priority for the attention of the e-Nose company. This priority setting is based on the consequences when the force will be ignored and the extent of influence the e-Nose company can conduct in order to turn the force into an opportunity.

Certificates, proof of principle, and competitors are identified as critical barriers and are of the highest priority. These forces need to be dealt with in order to make a chance of entering a market. The introduction process in a hospital and reduction of time to identification are identified as high priority forces. Contracts and contacts, a broad application of the identification device and the possibility of identifying a broad range of pathogens are of medium priority. Internal politics and availability of funds, which the e-Nose company does not have much influence on, have a low priority.

9.2 Data synthesis

The relevant data, as described in 9.1, will be structured into strengths of the µDtect, weaknesses of the µDtect, and possible opportunities for further development. The main research question will be answered based on this synthesis.

Strengths

Low cost of ownership

Compared to other microbiology identification devices, the µDtect has a low cost of ownership. It has a lower investment cost, as well as a low operating cost. The performance of the µDtect on the "cost of ownership" criteria exceeds that of the competitors; only the cost of consumables of the MALDI-TOF/MS is lower than that of the µDtect.

In the Dutch clinical market the cost of ownership is not deemed very important for the decision of acquiring new microbiology identification technology. It is possible that in markets where funds and resources are scarcer, the costs are deemed of more importance.

Low chance of contamination

Each handling of the sample increases the chance of contaminating the sample. For bacterial pathogen identification with the µDtect there are no additional sample preparation steps required. The culture flask is placed in the µDtect, similar of placing it in the incubator like it is normally done, and besides the incubation and detection, identification takes place as well.

A smaller chance of contamination results in that less samples will be contaminated due to handling. Less contamination results in a more accurate diagnosis of which bacterial pathogens are present in the patient. Therefore, the prescription and use of antibiotics can be done and managed more accurate.

Ease of implementation

The µDtect is easy to implement in the current clinical microbiology identification process in the Dutch market. It combines the incubation step with the identification step with the use of flasks that are currently used. The identification of bacterial pathogens does not require additional preparation steps, which makes the µDtect very easy to use compared to other identification devices. After the diagnosis with the µDtect the sample can be used for further testing.

Weaknesses

Low accuracy

The accuracy is deemed the most important criterion when making a decision about acquiring a new clinical microbiology identification device. The performance of the µDtect on the identification accuracy on the four most important bacterial pathogens is the lowest compared to the competing technologies. For the introduction of the µDtect to the Dutch market a high accuracy (at least 95-98%) is required.

Only works for blood samples

Currently the µDtect is only able to diagnose blood samples. The reason for this is that blood samples are sterile in nature, and only one bacterial pathogen is responsible when infected. In, for example urine or saliva samples, more bacterial pathogens are present. The µDtect has problems with

identifying samples with polyflora, because the “smell” of one species of bacteria can cover the “smell” of another which can be the cause of the infection.
Being able to only diagnose blood samples limits the applicability of the µDtect, and reduces the competitiveness compared to technologies which can identify a broad range of samples.

Ability to detect only a limited range of bacterial pathogens
Currently the µDtect can only identify a limited set of bacteria with reasonable accuracy (80 – 90%). Especially the Gram positive pathogens are difficult to identify for the µDtect (Appendix 1) and three of the four most important pathogens are gram positive. In order to be able to be competitive in the Dutch market the µDtect should be able to identify at least the four most important pathogens with a high accuracy (95 – 98%). This performance should be proven in clinical trials with patient materials.

Not yet certified
To be able to introduce the µDtect to the market certification is required. Most countries have its own agency and set of qualifications to which the device has to comply to in order to be allowed onto the market. The process of certification will take time and resources.

Opportunities for development
There are several directions for development which can increase the competitiveness of the µDtect. These opportunities are based on the current development and performance of the µDtect and the market requirements of the Dutch clinical market.

Accuracy
For the Dutch clinical market identification with accuracy of 80 – 90% is not high enough. The accuracy of identification of individual bacterial pathogens within a blood sample should be at least at 95%. With accuracy below 95% microbiology physicians cannot rely on the test results and tests need to be done for confirmation.
In this stage of development of the µDtect there is a long way to go in order to be able to identify a broad range of bacterial pathogens with high accuracy. Therefore, focus the development on certain bacterial pathogens can be required. There are several options for the focus of the development: focus on the “easy to smell” bacterial pathogens, focus on the most important bacterial pathogens, or focus on exceptions of bacterial pathogens.
By focusing the development on the “easy to smell” bacterial pathogens can help an early proof of principle. The proof that the µDtect can identify certain bacterial pathogens from patient samples is a requirement for entering the market. The proof that the principle of the µDtect works can heighten the interest in the µDtect at an early stage and it is the first step of convincing the key stakeholders of the use of the µDtect.
Focus the development of the µDtect on the important bacterial pathogens in order to identify them accurately is a market requirement for the µDtect to become the routine identification device. For the Dutch market the Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, and the Eschericha Coli are the important bacterial pathogens. Currently the µDtect is not able to identify these microorganisms with high accuracy. Therefore, it is likely that it will take considerable time and effort to achieve this.

It is also possible to focus the development of the µDtect on the exceptions of bacterial pathogens. With exceptions is meant: bacterial pathogens which are hard to detect with other identification devices. Diversification can avoid that the µDtect has to compete with an already well established microbiology identification device. Which the exceptions are is dependent on the region.

Broad range of samples

Currently the µDtect is not able to identify several pathogens simultaneously in a sample with poly-flora. The strongest smelling bacterial pathogen covers the smell of other microorganisms. Being able to identify the microorganisms present in a poly-flora sample is required for the analysis of sample other than blood samples.

Not all microorganisms present in the poly-flora samples are the cause of the infection. The pathogenic bacterium that causes the infection, for example urinary tract infection, is often present in a multitude of its normal level. Therefore, in order to be able to identify the cause of an infection the µDtect should be able to quantify the microorganisms present in the sample.

Therefore, in order to be able to diagnose other samples beside blood samples, the ability to identify bacterial pathogens in a poly-flora sample and quantification needs to be developed.

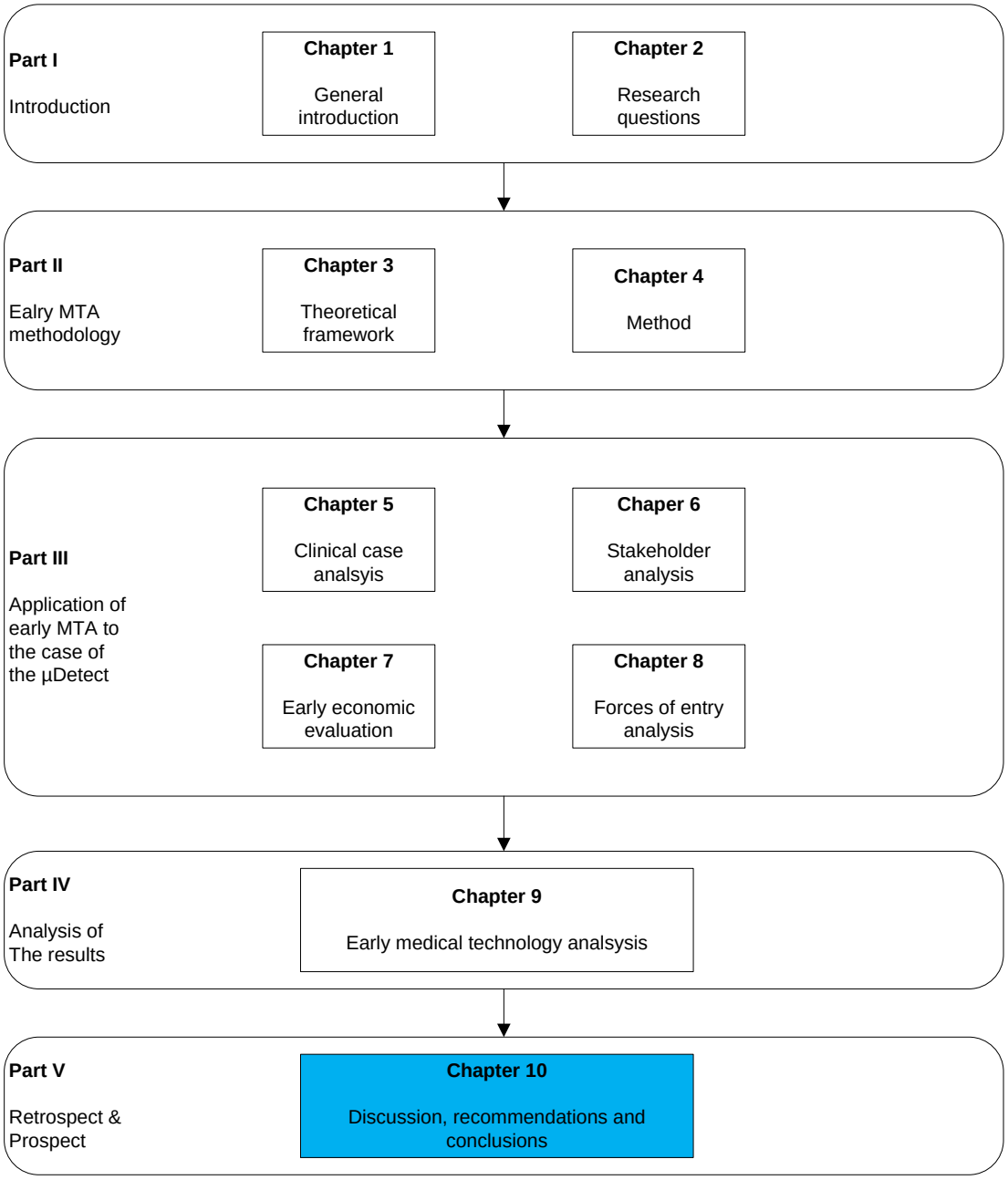
Faster identification

The faster a bacterial pathogen is identified the better, because the antibiotics treatment can be specified based on the identification. This reduces chances on side effects and immunization. In a typical Dutch hospital the reconsideration and possible adjustment of treatment is done once or twice a day. Therefore, an identification that is only a few hours faster than the current procedure with the MALDI-TOF/MS, will not have much added value. The reduction of the time of identification needs to be considerable (at least 6 hours) in order to be an added value which is worth for acquiring a new identification device. Currently the µDtect is about four hours faster than the conventional method with the MALDI-TOF/MS, which requires a cultivation step of four hours. Although, a fast identification procedure can be done with the MALDI-TOF/MS. This fast procedure would make it almost as fast as the µDtect, although this test is more expensive (€10 - €12) and less accurate (70 – 80%) than the conventional method.

Improving the time to identification will improve the competitive position of the µDtect on the (Dutch) market.

Part V

Retrospect & prospect



10 Discussion, recommendations and conclusion

This chapter starts with a discussion about this research (10.1). The methods used in this research will be evaluated and limitations addressed. It is followed by the recommendations for the development of the µDtect and further research (10.2). This chapter ends with the conclusion of this research (10.3).

10.1 Discussion

The µDtect is a product in an early stage of development. Therefore, there is still uncertainty about the impact of the device on the effectiveness and efficiency of the microbiology identification process. The identification technology is based on the electronic nose technology, which can be used to "smell" volatile compounds in the air. The aim of this study was to identify where in the current clinical pathway the µDtect should be situated and to indicate on which aspects the development of the µDtect should focus in order to get the highest potential clinical and commercial value. Addressing this aim an early medical technology assessment (MTA) has been conducted. The early MTA consisted of four analysis parts: the clinical case analysis, stakeholder analysis, early economic evaluation, and forces of entry analysis. These four analysis methods are applied in order to make a broad assessment. The use of multiple methods makes it possible to triangulate the data.

A clinical case analysis was carried out to determine the potential place in the clinical setting for the µDtect, identify which bacterial pathogens are of importance, and the potential competing technologies with their general strengths and weaknesses. The clinical case analysis provided the context of the research. The clinical microbiology laboratory was identified as a potential place in the clinical pathway of microbiology diagnosis. At this place the expertise and instruments for further testing are available. Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, and the Eschericha Coli were identified as highly important bacterial pathogens. The µDtect should be able to identify these with high accuracy in order to make a chance of being used routinely as a microbiology identification device.
Four potential competitors were identified with a general overview of their strong and weak points. These competitors are used as the alternatives in the early economic evaluation, in order to compare the performances against that of the µDtect.

A stakeholder analysis was carried out to determine which persons were the potential users and should know about the potential benefits, and which persons were in the position to decide on whether or not to purchase the µDtect. This is valuable knowledge when one wants to introduce a product to the market and for gathering further information about what is deemed important by these persons. The results indicated that there are key stakeholders within both processes. Microbiology physicians and laboratory managers make the decision whether or not to submit a request for purchase through a business case. These stakeholders should be convinced of the added value of the µDtect in order to initiate the purchase process. The head of the department and the hospital management have the influence to make the final decision on the purchase based on the advice of an advisory commission. For the process of using the µDtect the microbiology physician and the analyst are key stakeholders and therefore important for the determination of what is deemed important.

An early economic evaluation has been conducted to evaluate the current performance of the µDtect. The performance of the µDtect is compared to that of the competitors as identified in the clinical case analysis. The decision criteria, on which the performance of the alternatives is measured, were identified by the stakeholders of the purchase process. A MCDA is conducted in order to measure the performance of the alternatives on attributes, and to identify which attributes are important for the purchase decision. The clinical performance was deemed most important, especially the attribute "accuracy". The categories "cost of ownership" and "impact on workflow" do have a lot less weight in the purchase decision.
This MCDA conducted in the early economic evaluation makes it possible to identify and evaluate the strong and the weak points of the alternatives. The results indicate that the strong points of the µDtect are in the categories of "cost of ownership" and "impact on workflow". A weak point of the µDtect is the accuracy.

The last part of the early MTA consists of a forces of entry analysis. In this analysis the possible introduction barriers and opportunities for the µDtect are determined. A prioritization of forces has been made based on the influence the e-Nose company has on the force and the potential consequences for the introduction of the µDtect when the force is ignored. Three critical forces have been identified: certification, proof of principle and competitors. These forces have to be taken in consideration when making decisions about the development and introduction of the µDtect. The introduction process of the hospital and the reduction of time to identification are important factors which have influence on the introduction of the µDtect. The time to identification, the possibility of identifying a broad range of samples, and identify a broad range of pathogens with high accuracy, are identified as forces which possibly can be dealt with through development of the µDtect.

The data of these four parts are brought together and synthesized. Together they form the early MTA. These four methods all show different aspects which are important for decisions about the development and a potential introduction of the µDtect to the market.
Altogether, the results show that the µDtect potential place in the clinical pathway is in a clinical microbiology laboratory. The strengths of the µDtect are within the categories "cost of ownership" and "impact on workflow" and a reduced chance of contamination. When selecting a market for the introduction of the µDtect these aspects should be kept in mind.
The weak point of the µDtect is the relatively low accuracy. To be used in a Dutch laboratory routinely the accuracy of the µDtect need to be improved considerably (95% or more) for at least the Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae, and the Eschericha Coli.
For further development of the µDtect there are several options. The development can focus on increasing the accuracy, being able to quantify and identify poly-flora, and/or decrease the time to identification. An increase in accuracy seems to be a prerequisite in order to be able to enter the market. With a lower accuracy than the MALDI-TOF/MS the chances for the µDtect to enter the Dutch clinical market are slim. It can be expected that markets outside the Dutch market deem the accuracy of the identification device an important criterion as well.
For increasing the accuracy the research can focus on "easy" to identify bacterial pathogens, the four important pathogens, and/or exceptions. It is expected, considering the current ability of identification of the four important pathogens, that being able to identify these with high accuracy will take a considerable amount of time and resources. Focusing on "easy" pathogens probably

results in an earlier proof of principle which can increase the awareness of the µDtect under stakeholders.

10.1.2 Limitations of the methods

The clinical case analysis has several limitations. The first limitation is that the potential places for the µDtect in the current clinical pathway are identified by persons who work in or closely with a clinical microbiology laboratory or hospital. These persons may have difficulties in imagining that an identification device can be used outside laboratories and/or hospitals. Therefore the respondents can have a biased view.
Second limitation of the clinical case analysis concerns the identification of important bacterial pathogens. The identification is done based on data from Dutch hospitals. The epidemiology differs between areas. In urban areas other pathogenic bacteria are more frequent than in rural areas. Between countries and climates the differences will be even more distinct. Therefore the important bacterial pathogens identified in this research only apply for the Dutch market.
The third limitation of the clinical case analysis is that the competing technologies are based on the general description of the technologies. Within the technologies there are a lot of variations possible. For example the Raman spectroscopy can be fitted with an infrared laser or an ultra violet laser, with SERS or without. These variations have effect on the performance of the alternative.

A limitation of the stakeholder analysis is that there were only a limited number of respondents. The respondents were selected from Dutch clinical microbiology laboratories and hospitals. Therefore, the results may be too limited for broad generalizations.
The stakeholder analysis is based on the salience model. This model and typology has not have been used often for the health care setting. There can be concerns that the typology, which is a businesslike typology, is not applicable for the health care setting. Although it can be argued that the health care sector is transforming into a health care market with an increase in businesslike aspects.

The early economic evaluation has several limitations considering the identification of the attributes and assessing their weights, and on the measurement of the performance.
The identification of the attributes and assessing their importance is done based on the information of a limited number of respondents. Therefore the results may be too limited for generalizations. The identification of the decision criteria is done in a short period of time during each interview (5 -10 minutes), this due to time constrains. The possibility remains that not all relevant attributes are identified.
Some of the attributes may covariate with each other. For example the purchase price and the maintenance cost. It is not uncommon that expensive devices have a higher maintenance costs, 10% of the purchase price is a rule of thumb for estimating the maintenance costs [89].
The preferences are determined for a clinical microbiology identification device in general, but these preferences may chance dependant on the situation and the pathogen under consideration. Further the preferences are elicited from respondents in the Netherlands. In other countries the preferences may differ, therefore they cannot be generalized.
There are some limitations to the measurement of the performance of the alternatives on the attributes. The accuracy of an alternative is based on an average of the accuracy of identification of a few bacterial pathogens. It is likely that the accuracy is not evenly important for each pathogen.

Assessing the performance on the accuracy for each pathogen separately would give a more accurate view of the performance of the identification device.
A microbiology detection and identification device, such as the µDtect, has been compared to several identification devices (MALDI-TOF/MS, Raman spectroscopy). The MALDI-TOF/MS and the Raman spectroscopy are only used for testing samples which are already flagged as positive. Therefore, only accuracy plays a role. For the µDtect, which handles negative samples as well, specificity plays a role as well.

As with the other parts, the forces of entry analysis has been done based on information from a limited number of respondents. Therefore, generalizations of the identified forces should be made with caution. Some forces of entry, which were identified as market requirements, could also be handled as attributes.

10.2 Recommendations

This study was an effort in constructing a comprehensive approach to address and assess the potential of the µDtect and to support product development decisions. Based on this assessment several recommendations can be made. These recommendations encompass the strengths and weaknesses of the µDtect, development direction, further research, and the early MTA tools.

µDtect

This study is based on the information from the Dutch clinical market. Therefore, the weights of the attributes are based on the preferences of the Dutch market. It can be expected that markets in other countries have a different set of preferences.
The identification of the important pathogens is based on the occurrence of infections with the bacterial pathogens in the Netherlands. This epidemiology is area sensitive and therefore is likely to be different in other countries.
Due to the relatively low accuracy, which is deemed the most important aspect of a microbiology identification device, the chances for the µDtect to be implemented for routine diagnosis of blood samples in Dutch microbiology laboratories is slim. It is recommended to identify assess clinical markets in other countries on their preferences and epidemiology. Possibly markets can be identified which fits better with the strengths of the µDtect and have an epidemiology that can be identified with the required accuracy by the µDtect.

The early economic evaluation has been based on decision criteria and preferences elicited from persons working in the Dutch medical market. Due to time constraints the identification of attributes has been done in a short time (max 10 minutes in each interview). There is a possibility that decision criteria are missed because of the short time period. Conducting a group session with the advisory committee and several microbiology physicians would encourage a debate and therefore result in a more complete set of decision criteria.
The preferences are elicited from people who are stakeholders in the acquiring of new medical technology process. Although several positions are covered, eliciting preferences from all the stakeholder positions would give a more complete view. The preferences are elicited by means of the budget pie method. Eliciting preferences through pair wise comparison may provide a more robust set of preferences, because the consistency can be checked.

During the development phase there are a lot of uncertainties which make development decisions challenging. The direction of development is based on many decisions. It is recommended that before any decisions are made about the focus of the development of the µDtect, to evaluate the potential markets in more detail. The market requirements, important pathogens can differ for each market and can have a large impact on the development decision.

Early MTA

A combination of certain methods has been used in this study. There are plenty more tools and methods available which can be used to investigate different aspects. It is recommended that the e-Nose company explores the various other methods of early MTA during the development of the µDtect. Strategic business cases and real options analysis can help with the assessment of the potential markets.

From the analysis of the results, it became apparent that some information about the market was lacking. For example in the early economic evaluation; several of the competing technologies are still in the development phase and therefore estimations had to be made about their performance. This is reflected in the sensitivity analysis. The intervals used in order to deal with the uncertainty have a large impact on the overall performance of the alternatives. The utility score of the µDtect went from worst option in the worst case scenario, to the best option in the best case scenario. This indicates that the data is not robust. It is recommended that these estimations and intervals are reviewed when additional data becomes available.

The use of early MTA has proven to be relevant in providing direction of the product development. It helps to guide decisions, and structure possibilities. Where normally product development decisions are made on intuition or vision, the early MTA provides a toolbox to enable informed decision making. Therefore, it is recommended that the eNose company makes use of the early MTA toolbox for the development of the µDtect and other products.

10.3 Conclusion

In this research, an early MTA has been performed. The early MTA consisted of four parts: a clinical case analysis, a stakeholder analysis, an early economic evaluation and a forces of entry analysis.

The µDtect has the highest potential within a microbiology laboratory. The main reasons for placing it in a laboratory is that besides the identification of the species, the susceptibility of the pathogenic bacteria to certain antibiotics has to be determined as well. In a laboratory all the required tests and technology are available, as well as the expertise. Placing an identification device at another place in the clinical pathway, for example at another department like the IC or at a general practitioner is not preferred because of the lack of expertise and instruments.
The bacterial pathogens: Staphylococcus Aureus, Staphylococcus Epidermidis, Eschericha Coli, and the Streptococcus Pneumoniae are identified as the top four important pathogens that a microbiology identification device should be able to identify with high accuracy for the Dutch clinical market. The Staphylococcus Aureus is important because it is highly virulent, the other three because they are the most frequent pathogenic bacteria found in samples. Staphylococcus Epidermidis is the main source of contamination, because it lives on the skin. It can get in the sample by the needle that is used to draw blood from the patient. Although it is a contaminant in most of the cases it can be

dangerous for certain groups of patients when it is present in the blood. It is important that a microbiology identification device can identify this bacterium in order to monitor these patients.
Four technologies are identified as potential competitors: the MALDI-TOF/MS, the Raman spectroscopy, the real time PCR, and the Lab on a chip. The MALDI-TOF/MS is the current state of the art in Dutch hospitals.

The results of the stakeholder analysis show that the key stakeholders for the process of acquiring medical technology are the: microbiology physician, laboratory manager, head of department, and the hospital management. These stakeholders have great influence on the implementation of the µDtect and should be convinced of the added value. The microbiology physician and the laboratory manager initiate the purchase process and therefore should be approached first.
For the use of the identification technology the microbiology physician and the analyst are identified as key stakeholders. Their whishes and opinion on technical requirements should be taken into account when developing the µDtect.

In the early economic evaluation the performance of the µDtect is compared to the potential competitors. The results show the strengths and weaknesses of the µDtect compared to the competing technologies.
The strengths of the µDtect are in the categories “cost of ownership” and “impact on workflow”. In short this means that the µDtect is relatively inexpensive to acquire and operate, and fits well and is easy to operate and implement in the current clinical pathway. Another strength of the µDtect is a low chance of contamination because no sample preparation steps are required for identification.
A weakness of the µDtect is that it has a relatively low accuracy for identifying bacterial pathogens. This criterion is deemed most important in the Dutch market for the purchase decision.

In the forces of entry analysis, forces are identified which can become market entry barriers or market opportunities, depending on how they are handled. Certificates, proof of principle, and competitors are identified as critical barriers and are of the highest priority. Certificates have to be acquired in order to be allowed to introduce the µDtect to the market. Without a proof of principle key stakeholders will not consider the µDtect as an option. The µDtect needs to have added value compared to competitors in order to have market potential. The introduction process in a hospital and reduction of time to identification are identified as high priority forces. Contracts and contacts, a broad application of the identification device and the possibility of identifying a broad range of pathogens are of medium priority. Internal politics and availability of funds, which the eNose company does not have much influence on, have a low priority.

In conclusion, the µDtect is a device that has potential in a clinical microbiology laboratory. Entering the Dutch clinical market will be difficult for several reasons. The current standard set by the MALDI-TOF/MS is high. It has superior accuracy compared to the µDtect, and the reduction in the time to identification with the µDtect is not significant in order to be implemented for routine blood sample diagnosis. The major strength of the µDtect compared to the MALDI-TOF, and the other competitors is that it is relatively inexpensive in purchase and operation costs. Although, in the Dutch market the costs are not deemed so important for the purchase decision, this may be different in other countries. Markets which have less funds available can be of interest for the µDtect.

The accuracy is currently the greatest weakness of the µDtect. Further development should focus on increasing the accuracy of the µDTect. It is dependent on the epidemiology of the market which pathogens to prioritize for development.

It can be expected that increasing the performance to the required levels for these pathogens will cost a considerable amount of time and resources. A proof of principle for accurate identification with patient material still has to be delivered. Delivering this proof of principle by focusing the development on the pathogens which the µDtect will likely be able to identify with high accuracy can heighten the attention for the µDtect which can open up market opportunities. The strategic choice of which pathogens to target for further development depends on the market the eNose company wants to enter.

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Appendix 1

Current identification potential µDtect

GN	Escherichia	coli
	Klebsiella	oxytoca
		pneumoniae
	Morganelle	morgani
	Proteus	mirabilis
	Pseudomonas	aeruginosa
	Salmonella	enteriditis
		typhimurium
	Serratia	marces
	Stenotrophomonas	maltophilia
GP	Enterobacter	aerogenes
		cloacae
	Enterococcus	faecalis
		faecium
	Staphylococcus	aureus
		epidermidis
	Streptococcus	anginosus
		mitis
		oralis
		pneumoniae
		beta-Gr A
Yeast	Candida	albicans
		glabrata
	Cryptococcus	
Mold	Aspergillus	

	75-95
	65-75
	60-80, based on limited set of subspecies
	30-60, ongoing work
	Unknown, work in progress
	Unknown, not measured