Master Thesis Health Sciences

July 2011

Potential of novel lab-on-a-chip technology in current and future healthcare settings: a clinical case assessment.

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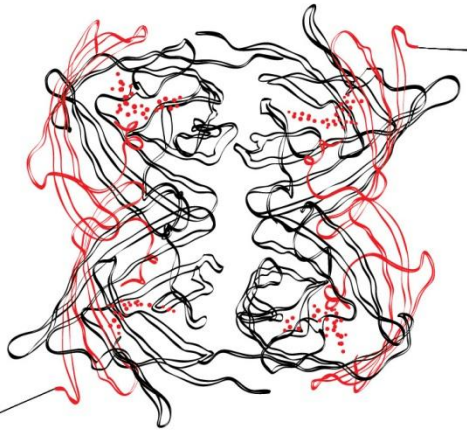

UNIVERSITEIT TWENTE.

Potential of novel lab-on-a-chip technology in current and future healthcare settings: a clinical case assessment.

An explorative study towards the potential use of a lab-on-a-chip as patient self-test, in the primary and hospital care of the Dutch healthcare system.

Master thesis
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School of Management and Governance
Master: Health Sciences
Track: Health Services and Management
Date: 6 July 2011
Place: Enschede
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Samenvatting

Achtergrond - Technologie krijgt een steeds grotere rol in de Nederlandse gezondheidszorg, zowel op diagnostisch als therapeutisch gebied. Eén van de recente ontwikkelingsgebieden is de nanotechnologie, waarmee het mogelijk is om metingen aan de mens te doen middels kleine laboratoria op een chip, genaamd lab-on-a-chip. De lab-on-a-chip van deze studie heeft tot doel middels het meten van kreatinine in bloed, de screening en monitoring van de glomulaire filtratie snelheid in de nieren en daarmee ook de nierfunctie te bepalen. Echter omdat er bij deze lab-on-a-chip sprake is van een zogenaamde technologie-pushed innovatie is er nog weinig duidelijkheid over de gebieden binnen de Nederlandse gezondheidszorg waar deze chip gebruikt kan worden. In het Nederlandse zorgsysteem zijn daarom de drie belangrijkste toepassingsgebieden, namelijk zelfmonitoring, 1e lijns zorg en 2e lijns zorg onderzocht. Dit onderzoek is uitgevoerd volgens de 'clinical case' analyse.

Doel - Het doel van dit onderzoek is het identificeren van de mogelijkheden van een nieuwe lab-on-a-chip technologie om biomarkers te meten bij nierziekte, relevant voor diagnose, screening en monitoring doeleinden.

Methode – Dit onderzoek is gestart, door middel van literatuur onderzoek, met het vinden van de grootste populatie binnen de populatie met nierfunctie verlies. Door middel van kwalitatief onderzoek (interviews en vragenlijstonderzoek) zijn de wensen en behoeften van patiënten en de specialisten in eerste en tweede lijn bepaald. Daarna is er voor het meest veel belovende gebied een voorlopig marktonderzoek uitgevoerd om daarmee meer inzicht te krijgen in specifieke locatie en populatie. Tevens zijn de populatie specifieke eigenschappen als gezondheids- en efficiëntie winst middels het toepassen van een lab-on-a-chip bepaald. De validiteit is getest middels pilot studies en vergelijkbaar onderzoek in de literatuur.

De analyse van de interviews, werd uitgevoerd door gebruik te maken van de bricolage methode. De vragenlijst ingevuld door de patiënten is geanalyseerd met het programma SPSS versie 18, waarbij verhoudingen en gemiddeldes bepaald zijn. Het scenario gedeelte van het voorlopige marktonderzoek werd geanalyseerd door gebruik te maken van ranking (Rank Sum Weights), het bepalen van de standaard deviatie en het 95% betrouwbaarheidsinterval in het programma Excel-2007. Utiliteiten met bijbehorende standaard deviaties en betrouwbaarheidsinterval werden gegenereerd middels het programma SPSS-18. De uitkomstmaten (gezondheid, geld en tijd) van het tweede gedeelte van het voorlopige marktonderzoek werden toegepast in een zogenaamde terugvouw-boom. De validiteit van de analyse is overeenkomstig met eerder onderzoek.

Resultaten – In de literatuur werd beschreven dat binnen het gebied van zelf-testen en eerste lijnszorg de populatie bestaande uit patiënten met Diabetes Mellitus (DM) type 2, de grootste populatie is gerelateerd aan nierfunctie verlies en bekendheid met zelf-monitoring. Verder is duidelijk dat DM zich kan ontwikkelen tot totaal nierfalen met de bijbehorende grote gezondheids- en economische gevolgen. In de tweede lijns zorg, zorgt het toenemende aantal contrast CT scans voor een grote populatie patiënten die risico loopt op nierfunctie verlies.

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Het kwalitatieve onderzoek onder huisartsen (n=7) geeft sterke aanwijzingen dat het verschil tussen de toepassing bij point of care zorg waar de lab-on-a-chip zich op richt en het verloop van nierfunctie verlies bij diabetes mellitus te groot is. Op dit gebied zien de huisartsen geen mogelijkheden voor het gebruik van de lab-on-a-chip. De huisartsen zien de aanschaf van de lab-on-a-chip in hun praktijk alleen als optie wanneer de huidige financiële regelingen veranderen. Als de huisartsen gedwongen zijn te onderhandelen over prijzen, dan kiezen ze de voor hen makkelijke weg, namelijk het zelf uitvoeren van de tests.

De patiënten survey onder een deel van de Diabetes Mellitus populatie (n=22) geeft aan dat hoewel de exacte gewenste screeningsfrequentie van de nierfunctie bij patiënten met Diabetes Mellitus wisselt per geslacht en leeftijd de algemene trend is dat de huidige gouden standaard van één maal per jaar als te laag wordt ervaren. De meningen van de patienten met DM zijn verdeeld over de gewenste locatie van de lab-on-a-chip, het gebruik als zelf-test, of als test binnen de huisartsenpraktijk. Echter zien veel mensen de lab-on-a-chip alleen geschikt wanneer het een volledige vervanging van het huidige lab is.

De resultaten van het kwalitatieve onderzoek onder laboranten en radiologen (n=11) laten zien dat er op de afdeling radiologie belangstelling is voor het gebruik van een snel medium ter bepaling van de nierfuncties bij patiënten die komen voor een contrast CT scan.

Het voorlopige marktonderzoek onder radiologen en laboranten (n=42) uit verschillende ziekenhuizen (n=4) heeft aangetoond dat er een significante voorkeur is voor de inzet van de lab-on-a-chip bij semi-acute en geplande patiënten. Voordelen voor de semi-acute patiënten zijn een verbetering in gezondheids- en tijdswinst en bij de geplande patiënten bij de tijdsefficiëntie. De acute patiënten populatie wordt niet gezien als een geschikte populatie voor het gebruik van deze technologie, omdat deze groep altijd gescand wordt, ongeacht de nierfunctie.

Conclusie – Op basis van dit onderzoek kan worden geconcludeerd dat, er in de eerstelijns zorg op het gebied van Diabetes nauwelijks vraag is naar het gebruik van de lab-on-a-chip technologie. Er is een te grote discrepantie tussen de langzame progressie van de ziekte zonder de noodzaak direct de nierfunctie vast te stellen en de wens tot toepassing van point of care diagnostiek van de lab-on-a-chip. Een groot deel van de patienten met Diabetes Mellitus ziet de implementatie van de lab-on-a-chip in de thuis situatie als een meerwaarde. Echter bij deze toepassing worden er eisen aan de verantwoordelijkheid en feedback mogelijkheden gesteld, zoals controle en zekerheid. De meeste kans op een succesvolle implementatie en gebruik van de lab-on-a-chip is binnen het ziekenhuis ten behoeve van patiënten die een contrast scan ondergaan. De lab-on-a-chip kan voor semi-acute en geplande patiënten voordelen bieden ten opzichte van het huidige protocol in termen van gezondheids- en efficiëntiewinst.

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Summary

Background - Technology plays an increasing role in Dutch healthcare, both in diagnostic and therapeutic areas. One of the recent areas of development is the nanotechnology, which enables us to measure levels in the human body by little laboratory on a chip, the lab-on-a-chip. This chip in this study is development to measure creatinine in blood for screening and monitoring of the glomerular filtration rate in the kidneys, e.g. the kidney function. However, because this device is developed with a so-called technology-push strategy, there is little clarity about the most promising application within the Dutch healthcare where this chip could be used. There are three possible areas of application, self-monitoring, primary care and hospital care. The research is done following the clinical case analysis.

Purpose - The goal of this research is to identify the potential of a novel lab-on-a-chip technology to measure biomarkers in kidney disease relevant for screening, diagnostic and monitoring purposes.

Method – This study started, by means of a literature study, to determine the largest sub-population of patients within the group of patients with kidney dysfunction. Qualitative research (interviews and a patient survey) determined the needs and wants from patients and specialists in primary and hospital care. When the most promising area is identified, a preliminary market research will be done to gain more insight in the specific location and population as well as the health and efficiency benefits. The validity of the interviews and surveys is tested with pilot studies and by comparison with other studies in the literature.

The analysis of the qualitative study was carried out by using the bricolage method. The questionnaire completed by the patients was analyzed with the SPSS application version 18, ratios and averages were determined to support conclusions drawn. The scenario section of the market survey will be analyzed using ranking methodology (Rank Sum Weights), standard deviation and 95% confidence levels by use of the Excel-2007 application. Utilities and related standard deviations and confidence level were generated by use of the SPSS-18 application. The outcome measures (health, money and time) from the second part of the preliminary market research were applied in a so-called folding-back tree.

Results – Survey of the literature has shown that within the field of self-testing and primary care, the population consisting of patients with Diabetes Mellitus (DM) Type 2, is the largest population related to renal impairment and familiarity with self-monitoring. It is also clear that DM can develop into the worst form of renal failure with major health and economic consequences. In hospital care, the increasing number of contrast CT scan induces another group at risk for kidney dysfunction.

Qualitative research among general practitioners (n = 7) demonstrated that the difference between the point of care, which is the focus of the lab-on-a-chip, and the chronic progression of DM to kidney dysfunction is too large. There are no health benefits for patients who are diagnosed within a minute as opposed to a diagnosis within 24 hours. Therefore GP's see no possibilities for using the lab-on-a-chip in this area. The GP's only see implementation of the lab-on-a-chip in their medical

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practice as an option when the current financial system changes and they are forced to negotiate about the prices for the test they request.

The patient survey (n = 22) showed that although the exact desired frequency on screening of the kidney function in patients with DM varies with gender and age, the general trend is that the current standard of once a year is perceived as too low. The opinions are divided whether the lab-on-a-chip should be used as a self-test or whether it should be implemented as a test in the current medical practice. These differences are especially found between different age groups. In addition, many people see successful implementation of the lab-on-a chip, when it is a replacement for the current lab. The urgency of a replacement instead of an additional is very high.

The qualitative survey among radiographers and radiologists (n = 11) showed that there is an interest within the radiology department for the use of a fast medium to determine the renal function in patients who need a contrast CT scan.

The preliminary market research among radiologists and radiographers (n = 42) from various hospitals (n = 4) showed both a significant preference in relation to the semi-acute and scheduled patients and the use of the new device. These benefits for the semi-acute patients can be found on the areas health benefits and time efficiency and for the planned patients on time efficiency. The acute patient population is not considered to be an appropriate population for use of this technology; this group will always be scanned without hydration, regardless of renal function.

Conclusion - In the field of primary care there is little demand for the use of this lab-on-a-chip technology. The difference between the slow chronic progression of the disease and the point of care application of the test is too large. A large part of the diabetes mellitus population sees possibilities in using the lab-on-a-chip as a self-test, even though the clinical benefits are small. However, there are some requirements for accountability and provided feedback. The best chances for successful implementation and use of the lab-on-a-chip is introduction in the hospital in favor of patients who need a contrast CT scan. The lab-on-a-chip can offer benefits for semi-acute and scheduled patients in comparison to the current protocol in terms of health and efficiency benefits.

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Preface

Mobility and health are two of the most important factors of a person's wellbeing. During my study technical medicine I have learned a lot about technology and patients, but not so much about the financial and organizational aspect. The study Health Sciences and the thesis related to both my studies gave me the opportunity to investigate this side of the Dutch healthcare system.

Under the guidance of three supervisors, Dr. Janine van Til, Prof. dr. Maarten IJzerman and Prof. dr. Ron Kusters, I have completed this Master Thesis. I would like to thank them for their guidance and assistance during my research.

Their expertise in different areas contributed to a better result. I would also like to thank all of the people that I have interviewed and those who have helped me to complete this project: the radiologists, the radiographers, the general practitioners and the patients.

Above all I would like to thank my parents, Martin and Antoinette. They were my primary source of practical information on many occasions and they have helped me to find specialists and patients for my interviews and market-research. Not always content related, but nonetheless very important for my own mood, were my fellow graduates and my boyfriend. They helped me through this very busy and strict time schedule. I can say I am a lucky girl for having the best family and friends.

Anique Grob

July 2011

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1. Introduction

1.1.Healthcare and technology

Technology is increasingly important and more often introduced in healthcare. New technologies and improved technologies have the promise to better diagnose and treat patients. The process of developing and implementing a proper technology in a specific field, generally involves the cooperation of a multidisciplinary environment [1]. This introduction of new technologies to healthcare is widely recognized as a complex process [2]. One of the recent areas of interest within healthcare and technology, the nanotechnology, seems to offer new possibilities for healthcare improvement.

Nanotechnology is a rapidly expanding field, focused on the creation of functional materials, devices, and systems through the control of matter on the nanometer scale. Evaluation of the field by scientists leaves little doubt that nanotechnology is going to lead to a major revolution that is going to have a significant impact on society [3]. Over the past few years expenditures on research and development in nanotechnology have increased dramatically [4].

Within the field of nanotechnology, the development of the so called lab-on-a-chip is of interest to this study [5]. The term lab-on-a-chip is short for a miniaturized (bio) chemical analysis on a chip. The lab-on-a-chip technology started scientific development 15 years ago. This development gradually attracted other actors such as businesses and end-users [6]. Lab-on-a-chip devices can best be compared to the self-monitoring glucose device that diabetics use to monitor the glucose levels in their blood. An example of a lab-on-a-chip, with the same production properties as the lab-on-a-chip in this study, is developed to measure lithium levels [7]. The lithium levels are important for chronic depressive patients.

The lab-on-a-chip investigated in this study is still in development. The purpose of the lab-on-a-chip is detection of kidney dysfunction by measuring the creatinine levels in blood. When lab-on-a-chip is mentioned, the creatinine chip is meant. These creatinine levels present information on the (dys) function of the kidney. The best overall index of renal function in health and disease is traditionally considered the glomerular filtration rate (GFR) [8]. Because GFR is difficult to measure in clinical practice, most clinicians estimate the GFR from the serum creatinine concentration [9, 10]. Creatinine is a break-down product of creatinine phosphate in muscle, and is usually produced at a fairly constant rate by the body. Creatinine is filtered out of the blood by the kidneys (glomerular filtration). If the filtering of the kidney is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which reflects the estimated glomerular filtration rate (eGFR).

The lab-on-a-chip (in development) in this study works by a process called capillary electrophoresis. During this electrophoresis the lab-on-a-chip separates substances based on size and charge. This is done by small capillaries that are filled with an electrolyte. There are two basic steps, first is the loading of the sample (blood or urine), called the injection stage, followed by phase two in which an electrical current is set to the sample, to start the analysis. Conductivity detection then determines the concentrations of the substance in the sample. The goal is to perform this measurement within a

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few minutes. This technology makes it possible to perform measurements of substances such as blood or urine outside the hospital. Price (2001) describes that this point of care (PoC) testing has improved outcomes on morbidity and mortality. It is also demonstrated that PoC testing improved patient motivation to follow the treatment and satisfaction with the gained outcome. Therefore increasing the compliance to the treatment [11].

Even though several sources stress the positive effect of the lab-on-a-chip on a patient's life, there is only a small request from the market towards this technology The present situation can be characterized by the first successful applications, e.g. laboratory electrophoresis chips and portable blood analysis systems, together with an intense search on where the state-of-the-art technology can be made feasible and stimulate more economic activity. The state of the field is still merely scientific, but has also attracted quite some business interest. At the same time, commercialization, standardization and actual use are hard to find [6]. Technology that is developed without the described request from the market is called a technology-driven application. [1] It is required to identify the most likely way of implementation for these innovations, to improve chances of success [12]. When this information would be missing at time of implementation, implementation could fail or the incorrect patient population would be served.

One of the recent frameworks within industry to support strategic and long-range planning is the technology roadmapping. This approach is developed to provide structured and often graphical means for exploring and communication the relationships between evolving and developing markets, products and technologies over time [13]. Such a technological roadmapping can contribute to develop a business case analysis. The framework gives answers to the question whether the development fits the company strategy and product portfolio. It also describes the competitive advantages. Related analysis methods are SWOT and PEST analysis (Figure 1).

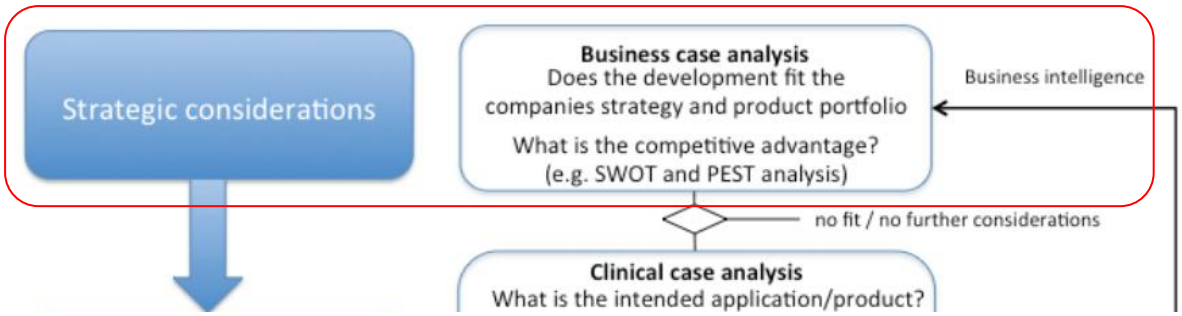

Figure 1 Strategic consideration – Part of Planning of medical product development by IJzerman and Steuten 2011 [14].

The business case analysis is also seen as the strategic considerations. A technology roadmapping provides the researcher with a business case analysis. It however does not answer the goal of this research. Which is to identify the potential of a novel lab-on-a-chip technology to measure biomarkers in kidney disease relevant for screening, diagnostic and monitoring purposes. Questions related to which population is the target group, comparator interventions and expected clinical outcomes and advantages need to be answered. A business case analysis is not the part of strategic consideration of interest.

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1.2.Kidney disease

To determine the correct strategic consideration. The disease related to the lab-on-a-chip should be understood. The intended application of the lab-on-a-chip in development is kidney dysfunction. To determine the possible advantages, the disease on which the lab-on-a-chip has an influence should be understood. In the last two decades detection of dysfunction of the kidney is becoming more and more important. The disease was overlooked for a long time, but recently became one of the focus points of the Dutch Safety Management System (SMS). With kidney dysfunction as one of the focus point of the SMS, the relevance and importance is highlighted. Ignoring the problem of kidney dysfunction is no longer possible.

Symptoms of kidney dysfunction can vary from person to person. When kidneys fail to filter properly, waste accumulates in the blood and the body, a condition called Azotaemia. Someone in the early stages of kidney disease may not feel sick or notice symptoms. If the disease progresses, symptoms become noticeable. The list of symptoms as a result of kidney dysfunction is very long. Some common symptoms are anemia, hypertension, fatigue and edema.

Chronic kidney failure is measured in five stages (*Appendix 2*), which are calculated using a patient's estimated Glomerular Filtration Rate (eGFR). A persistent reduction in the GFR to less than 60ml per minute per 1.73 m^2 is defined as chronic kidney disease [15]. The most common consequence and only treatment is dialysis.

The following numbers give an overview of the magnitude of the disease. More than 8 million US adults have kidney disease stage 3 or worse, from which about 275.000 patients are in the so called final stage 'End Stage Renal Disease' (ESRD) [16, 17]. By the year 2030 more than 2 million people in the US will need dialysis or transplantation for kidney failure. [15]

The problem with kidney dysfunction is the difficulty regarding early recognition. The symptoms only become noticeable at a very late stage of the disease, when treatment options are limited [18]. The GFR is very important to the detection and staging of renal disease. The glomerular filtration rate describes the flow rate of filtered fluid through the kidney. The official and most valid measurement of the GFR is by a blood and urine test at the department of Nuclear Medicine at the hospital. During this test the patient will receive an infusion in the arm, through which a small amount of a slightly nuclear substance will be admitted. During regular times small blood samples will be collected and during the six hours of the test three urine samples will be taken. The samples are used to determine the GFR [19]. As can be expected this is a very time consuming and expensive way of determining the function of the kidney. A faster and efficient way of detecting the kidney function is by use of the so called estimated GFR. Therefore a blood sample is analyzed at the laboratory of the hospital, the serum creatinine levels are determined and computed with input of age, race, and gender. This formula is known as the MDRD-equation and can be found in *Appendix 2* [20].

In this study the technology, the development and the competitive advantage are not the primary focus. The question is which population (the largest population of patients suffering from kidney dysfunction as a primary disease, or as a consequence of another disease) could benefit from introduction of this lab-on-a-chip to the healthcare market, what are comparator interventions and

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what the expected clinical outcome is. These questions are answered in the clinical considerations of the planning of a medical product development (Figure 2). These clinical considerations, as discussed by IJzerman and Steuten 2011, are the primary focus of this study [14]. This study is a clinical case analysis of 'the lab-on-a-chip measuring kidney dysfunction'.

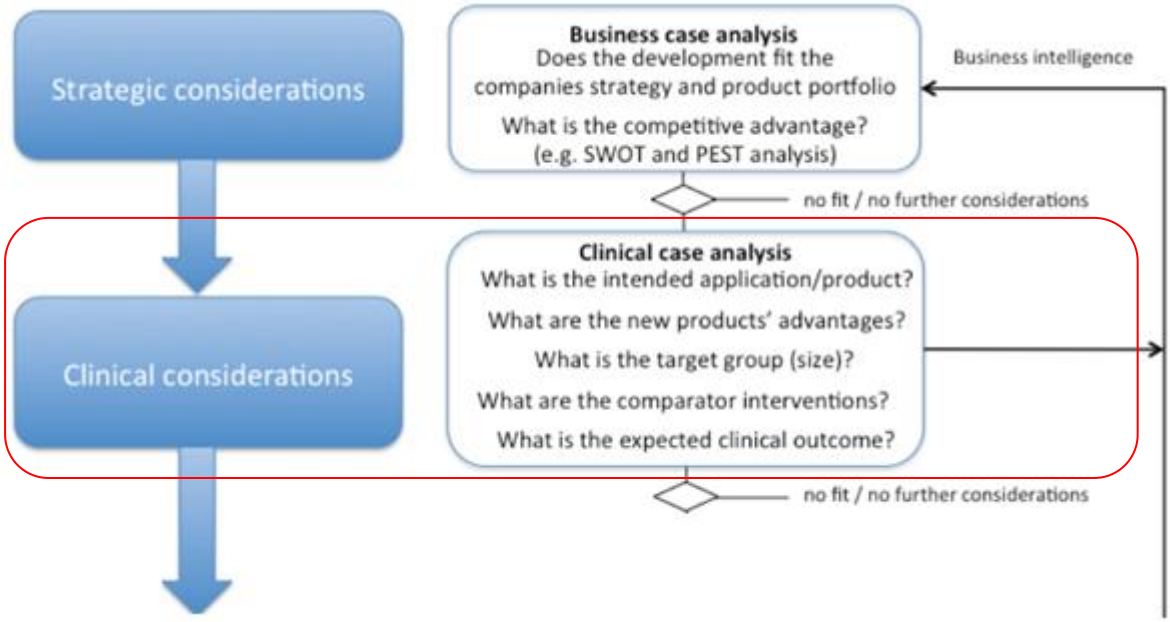

Figure 2 Strategic consideration – Part of Planning of medical product development by IJzerman and Steuten 2011 [14].

1.3 Needs assessment to identify possible applications

To identify whether the lab-on-a-chip could have a successful implementation, a needs assessment and inclusion of wants of patients in the sample population has been done. The lab-on-a-chip has multiple possible areas of implementation. The needs and wants of patients and professionals in healthcare are considered. This study therefore is a clinical case analysis, with the addition of a needs assessment. It uses multiple methods to analyze the application of the lab-on-a-chip.

The purpose of a needs assessment in health care, as defined by Stevens and Gillam in 1998, is to gather the information required to bring about change beneficial to the health of the population [21]. Improvements in health can be achieved by reallocating resources as a result of identifying four factors [21]:

- Non-recipients of beneficial healthcare interventions (unmet need)
- Recipients of ineffective health care
- Recipients of inefficient health care
- Recipients of inappropriate health care

In this study we are dealing with non-recipients of beneficial healthcare interventions, the unmet needs. The subjects of healthcare needs assessment are the populations and patients who are recipients or potential beneficiaries of health care. The assessment of individuals' needs form part of the assessment of a total population's needs.

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Besides the needs, this study also included the wants of patients. Literature is less clear on a definition for wants. In this study, the wants are defined as the non-necessary needs, but preferred changes to the healthcare system.

1.4 Research questions

The goal of this research is to identify the potential of a novel lab-on-a-chip technology to measure biomarkers in kidney disease relevant for screening, diagnostic and monitoring purposes. In this study, three possible branches are explored, namely the use of the device for self-monitoring, monitoring in a primary and hospital care settings.

A mix of methodologies was used to answer the research question of this study.

Which application of a lab-on-a-chip for measuring creatinine in blood for screening, diagnosis or monitoring of kidney function has the most potential in the Dutch healthcare?

- What is the population in which the lab-on-a-chip has the highest potential?
- What is the current practice with regard to screening and monitoring on kidney dysfunction in these patients?
- Is there a need to improve screening of these patients's decreased kidney function?
- Is there a want to change screening of this patient's decreased kidney function?
- What are the perceived benefits of the lab-on-a-chip technology compared to current treatment?

The Dutch healthcare system serves as a starting point. It is assumed that a study focused on the Netherlands, can be generalized to other countries.

Patients who could benefit from using this device are patients with a kidney dysfunction. However this is a very large population. Therefore the first sub-question investigates the largest population of patients suffering from kidney dysfunction as a primary disease, or as a consequence of another disease. The underlying idea is that the largest market represents the largest potential.

When the patient population is defined, a needs assessment can be performed. When introducing a technology to the healthcare system, patients and specialist will have to use it. Their wants and needs are included.

Related to the sub-population of patients with kidney dysfunction, the perceived benefits from using the lab-on-a-chip can be determined. These benefits could be measured in health or economic outcomes. The lab-on-a-chip might reduce the number of patients with contrast nephropathy, be more time efficient, less expensive or give less discomfort. These perceived benefits will be determined by the medical professionals.

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2. Methods

2.1.Introduction to clinical case assessment

To determine the potential clinical value of the lab-on-a-chip, a clinical case assessment has been done. In the assessment, several methodologies were used to identify possible application areas, patient and clinical needs, and the possible economic and health outcomes. For this research three cases of application, namely self-testing, primary care and hospital care are analyzed. This analysis was done based on size, clinical benefits of the patient population and the wants and needs of patients and professionals.

This section is structured as follows: This study started with a literature study to define the largest patient population with kidney failure. Then analyzed current practice regarding that particular patient group through literature research (guidelines and protocols) and by qualitative interviews. Following that, a needs assessment was performed using a patient questionnaire and interviews with specialists. The perceived benefits are identified through a preliminary market research using preferences assessment and decision analytic tools.

2.2. Identification of target groups

A literature research was performed to answer the question which patient population, within the group of patients with kidney dysfunction is the largest and best familiar with the lab-on-a-chip. Literature guidelines were assessed to determine the protocols used, thereby answering the theoretical part of the question, what is the current practice. The literature search was performed in Medline, using the MeSH terms: Lab-On-A-Chip Devices, kidney disease, nephropathy, primary healthcare and second line care.

2.3.Interviews

The interviews had multiple purposes. They were an addition to the literature search on current practice. The needs and wants of the specialists were determined. Finally, the interviews with specialist in hospital care gave an indication of the possible areas of perceivable benefits. These answers were the introduction to the preliminary market research.

The specialists, general practitioners for primary care and both radiographers and radiologist for second line care, were approached via contacts. To make sure that bias by location was prevented, the specialists were found across the Netherlands.

The interviews started with some general questions about the current practice in screening and monitoring patients with kidney dysfunction and satisfaction with protocols and possibilities in screening and monitoring. The familiarity of lab-on-a-chip devices was verified and additional information was given on the technology, substance detection possibilities and stage of development. In both interviews, the location of application was of relevance. Special attention was given to these questions on location. The interviews ended with the interviewer summarizing the gathered information as a check for completeness and correct interpretation. An overview of questions in the interviews can be found in *Appendix 4* for primary care and *Appendix 5* for hospital care.

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The interviews with the general practitioners, radiologists and radiographers had a qualitative focus and were semi-structured. They were performed to identify the wants and needs of the specialists and their patients. The interviews were conducted to gain insight in the agreement and disagreement of topics such as:

- Parameters of and requirements for the lab-on-a-chip
- The patient benefits
- The location of implementation of the lab-on-a-chip
- Who gets the responsibility
- The costs of purchase and use of the lab-on-a-chip.

The interviews were pilot tested by an interview with a general practitioner for the interview in primary care and by consulting specialists (a clinical chemist and the head of a radiology department) in the hospital care. This was done to find out if the questions were clear and complete. Subsequently, a few alterations to the interviews were made.

The data was collected in the months March till May. The specialists were invited to participate based on contacts and location in the Netherlands. Due to this way of selection a 'convenience sample' was created [22].

The analysis of the interviews was done by the so called 'bricolage' method. This method was used, because different techniques can be combined. The analysis started with a read through, to get an overall expression. Then the focus returned to specific interesting paragraphs, statements on attitudes were counted and connections between variables were found. [23]

2.4.Patient questionnaire

The patient questionnaire was conducted to determine the needs and wants of the patient population at risk for kidney dysfunction. The methodology of using a questionnaire to determine the wants and needs was used, because it gives a reflection of patients' expectations [24].

Patients were included based on their disease, which led to (possible) kidney dysfunction. There were no exclusion criteria based on age, race, gender or duration of the disease. The patients were included based on their 3-monthly appointment with the doctor's assistant at the GP medical practice.

The questionnaire consisted of 17 questions, developed by the author of this study. The questions were based on findings from the literature research and other background information. It started with gathering personal information, followed by information about patients' satisfaction with the current practice. The familiarity on the lab-on-a-chip was checked and when not familiar information was given by the doctor's assistant. Than the preferences towards self-testing and related conditions were questioned. Participation took the patients no more than 5 minutes. The entire questionnaire can be found in *Appendix 3*.

The questionnaire was administered face-to-face by a doctor's assistant at the GP medical practice. She was well informed, to make sure that the patients had the same information baseline. The questionnaire was both qualitative and quantitative. The qualitative information was used to compare the patients on baseline. To determine the familiarity on lab-on-a-chip technology and

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patient preferences in relation to the current practice and possibilities. The quantitative data was used to determine the desired frequency of screening for kidney function and the desire for self-testing versus screening at the medical practice.

The questionnaire was pilot tested on three patients in different age groups. It was also verified with a doctors-assistant. Subsequently a few alterations to the questionnaire were made.

2.5.Identification of potential application, health and economic benefits

The preliminary market research was done to answer the question on perceived benefits of the lab-on-a-chip technology compared to current treatment. Following the results from the interviews with the specialists in hospital care the preliminary research was constructed. Further research on this topic gave more information to identify the best match between lab-on-a-chip and population and location. This research was done through a preliminary market research, which gave information on the perceived benefits of implementation, both for the hospital (hospital care) and the patients.

The hospitals included in this preliminary market research are located across the center of the Netherlands (*Appendix 7*); location bias should therefore be excluded. The hospitals were selected based on size and location. Radiologists and radiographers were included because they are both closely related to the treatment of the patients with a decreased kidney function.

2.5.1 Identification of population and location

There are multiple methods to analyze a disagreement among specialists. It was important to not only identify the importance of the individual populations and location, but also to determine the effect when a population was related to a location. That is the situation that occurs in clinical practice. When performing a single analysis (without linking the population to location) the best individual location and best individual population, when combined, might not be a feasible combination in the clinical setting.

Based upon the results of the interviews seven scenarios were defined for the preliminary market research (*Appendix 6*). These seven scenarios described a clinical situation in which the use of the lab-on-a-chip on a specific location and to a specific population was simulated. The scenarios were composed that all clinical scenarios (as resulted from qualitative research) were described.

In this study a minimum of seven scenarios was necessary to relate to the clinical practice. Smith and Desvousges (1986) recommended that to ensure that respondents perform an effective ranking of the scenarios, four to six choices would yield the most consistent responses [25]. This study exceeds this limit with one more choice. In order to obtain a high validity a total of nine scenarios (two times three variables) should be presented to the specialist. Based on arguments from clinical specialists, who were concerned about relevance of two scenarios, the length of the study and the arguments by Smith and Desvousges, the total number of scenarios was reduced from nine to seven. The effect on the validity of the research and the generated outcome should be taken into account when analyzed. The ranking method itself was defined as a validated method in the article by Slothuus et al in 2002 [26]. That study showed that respondents are able to answer complex ranking questions, also when it concerns healthcare. In all seven scenarios the key words (the location and population) and a clinical example (aorta dissection, pulmonary embolism or abdominal scan) were highlighted to ease

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the discrimination between the different options. This lay-out was adopted from the paper by Phillips et al 2002 [27].

2.5.2 Identification of health and economic benefits

The second part of the preliminary market research contained seven individual questions on the chosen scenario. These questions gave information about estimations on benefits in health and time efficiency. The specialists were given three or four answer opportunities per estimation. This part also included a question to test the validity of estimations on incidence numbers of contrast nephropathy.

The methodology used to determine the perceived benefits is the decision tree model. Duncan defines the decision tree analysis as "*The process a manager can and should use in selecting the right structure to "fit" the demands of the environment, as well as the specific steps he or she can take to make the appropriate structure work*" [28]. The decision tree model in this study is used to assess the relative costs of multiple strategies, as is done by Yeoh et al in 2003 [29]. Decision tree analysis highlights patient subgroups and critical values in variables assessed. Importantly, the results are visually informative and present clear clinical interpretation about perceived benefits faced by specialists on patients in these subgroups [30].

The application Tree Age was used to determine the outcomes on time efficiency, costs and decreased discomfort. The Tree Age application is used in over 60 countries world-wide to build and analyze decision tree, Markov, comparative effectiveness, and cost-effectiveness models. The folding back method of the decision tree was used to compare the outcomes of current technology versus lab-on-a-chip.

2.6.Analysis

The analysis of the questionnaire was performed with SPSS-18. The application was used to plot graphs to determine the difference between location of choice and the desired frequency of testing. The information was split up by gender and age groups, to make differences visible and to define the group with highest preferences. Values determined were percentages per preference option. Determination of standard deviation was not included because of a low number of individuals in de sample population.

The forms retrieved from the preliminary market research were analyzed using attitude ranking. Many researchers have assumed that rankings of values are more valid than ratings of values because rankings forces participants to differentiate more incisively between similarly regarded values [31]. The ranking of scenarios was done on three levels. First the importance levels of the population versus location were determined. A total of 100% was divided on these two options. The 95% confidence interval generated by the SPSS-18 application gave the standard error of the mean and thus the upper and lower limits, the significance level, of the interval.

A second method on ranking was used to determine the best scenario (combination of location and population). In this study, the best scenario received the most points, the worst scenario (largest mismatch) the least points. The points could either be summed by dividing the point one to seven on the scenarios, as is done in the research done by Phillips et al in 2002. There the scores were based on a five point scale, with five points representing the most important attribute [27]. In this study

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however, the points were weighted before being summed. Therefore a total of one point was divided per specialist. The most liked scenario received 7 points, divided by 28 points (1+2+3+4+5+6+7), the second best received 6/28 points and so on [32]. This distribution of points is called Rank Sum Weights (RSW) [33] or Equi-Interval Weights (EIW) [32]. This methodology ensured that the interval between each consecutive weight was equal.

After summation of the points, they were divided by the total number of specialist who filled in the forms, to make better comparison possible. To draw valid conclusion the standard deviation and 95% confidence intervals were generated and graphically plotted in figures.

The standard deviation (SD or σ) of the values per scenario is defined by:

$$\sqrt{\frac{\sum (x-\bar{x})^2}{(n-1)}}$$

Figure 3 Excel 2007 - Equation standard deviation

In this equation, the standard deviation σ is the square root of the variance of X. So it is the square root of the average value sample divided by the size of the sample minus one. By using the SD and alpha set on 0.05, the 95% confidence levels were determined. The general equation for this interval is:

$$\bar{x} \pm 1.96\left(\frac{\sigma}{\sqrt{n}}\right)$$

Figure 4 Excel 2007 - Equation 95% confidence interval

In this equation, x is the sample mean, the value 1.96 is a result of the choice for the 95% confidence level, n represents the size of the sample and the standard deviation was derived from earlier analysis. The ranking, in combination with the SD and confidence interval gave results on importances of the scenarios. Thus combination of location and population.

The third ranking methodology was used to find the importance level of location versus population and the individual utilities per described location and population. To determine the importance levels of population versus location a one sampled t-test was performed. The One-Sample T-Test procedure tested whether the mean of a single variable differed from a specified constant. The standard deviation and 95% confidence levels are generated.

As performed in the study by Philips et al in 2002, the utilities were found through a ranking analysis [27]. In this study the utilities were introduced to the SPSS-18 application using the Means procedure. The Means procedure calculated subgroup means and related univariate statistics for dependent variables within categories of one or more independent variables. The utilities (individual preference for healthcare goods and services) for the three patient populations and locations were determined. The mean values and the standard deviation were generated.

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3. Results

3.1.Introduction

The three months of data collection resulted in 22 participating patients who filled in the questionnaire, 7 general practitioners, 11 radiologist and radiographers willing to answer the interview questions. Finally 4 hospitals with 12 radiologists and 30 radiographers participated in filling in the preliminary market research.

First, the results of the literature review are presented, from which the findings resulted in the identification of the population with high prevalence of kidney dysfunction. This population was the baseline for further research. Then the results found in self-testing and primary care will be presented. Results of second line care will be the final part of the results.

3.2.Literature review

A literature search to identify diseases and risk factors that increase the risk of kidney dysfunction was performed. The number of people affected with kidney dysfunction each year was determined and the results are shown in table 1. Glomerulonephritis and Tubulointerstitial disease were excluded based on a low incidence number and thus a relatively small market for implementation. The two main groups of interest, based on population size, were the patients with diabetes Mellitus (DM) or hypertension. The population of patients with hypertension is equal to the population of patients with DM. The difference is the probability of development of kidney dysfunction and familiarity with self-monitoring. This familiarity is high in patients with DM because of their self-monitoring of the glucose levels in their blood.

Primary disease	Prevalence	Probability of kidney dysfunction
Diabetes Mellitus	800.000 [34]	7%-16.4% [35, 36]
Hypertension	800.000 [37]	11.5% [36]
Glomerulonephritis	1.000 [38]	n.a.
Tubulointerstitial disease	3.300 [39]	n.a.

Table 1 Prevalence of primary disease and chance of development to kidney dysfunction

Diabetes Mellitus is a chronic disease, characterized by repeated high blood glucose levels. DM occurs in two forms, type 1 and type 2. 90-95% of the diabetes cases is DM type 2, [40] and is related to insulin resistance, decreased insulin secretion and increased hepatic glucose output [41]. Diabetes Mellitus is associated with the possibility of serious complications like Arthroscleroses, diabetes retinopathy and nephropathy (renal dysfunction).

The following information represents patients with DM worldwide. The numbers are slightly different per country because of different composition of the population, but give a good overall impression. Diabetes Mellitus is found in all age groups, but especially among people with an Indian, Black, Mediterranean or Asian background [35]. The gender [42], genetics [35] , insulin intake concentration [42] and type of diabetes [18, 35, 42] play a role in development of diabetes Mellitus. The estimated worldwide number of people suffering from diabetes is 250 million, with an expected growth to 380

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million people in 2025. Each year more than 3.8 million people die because of diabetes related causes worldwide.

3.2.1 Self-monitoring

For the DM population screening and monitoring, kidney failure is important because renal failure is the main cause of death in insulin dependent diabetic patients who have nephropathy [43]. Earlier research showed that technology can improve the self-care for diabetes. There is a need for additional trial research on the effect of existing and novel technologies, such as lab-on-a-chip, on diabetes related health outcomes. Novel technologies of interest are the lab-on-a-chip for determining the kidney function [44]. It is possible to decrease the chances of developing ESRD in the early stages of kidney dysfunction by patients, but early recognition of the disease is crucial [16, 45]. Diabetes is the leading cause of ESRD in many countries, and this population therefore is the largest potential market for a self-screening or -monitoring device for kidney dysfunction.

3.2.2 First line monitoring

The primary care in the Netherlands is the so-called entrance door for patients. Specialists that are part of the primary care are the general practitioner, the pharmacist, physiotherapist, home nurse, primary mental healthcare, midwifery and the dietician. The four main aims are accessibility, availability, continuity of care and comprehensiveness. [46]

The general practitioner is the primary care giver for chronic care patients and thus the patients with diabetes Mellitus type 2. There were a total of 8783 GP's in the Netherlands in 2008, of which 51% worked in a group practice (3 or more GPs), 29% worked in a duo practice and 20% in a solo practice [47]. There is a large market potential when introducing the lab-on-a-chip for kidney dysfunction to this market. Another key point of the current practice is the number of practice nurses present. Nowadays 40% works with a practice nurse. In relation to their working schedule, on average a GP sees 30 patients per day and makes 20 house calls per week.

3.2.3 Hospital care monitoring

Computed tomography (CT) is a painless, sophisticated x-ray procedure. Multiple images are taken during a scan, and a computer compiles them into complete, cross-sectional pictures. A CT scan obtains images of parts of the body that cannot be seen on a standard x-ray. Therefore, these scans often result in earlier diagnosis and more successful treatment of many diseases. [48]

CT scanning was developed during the mid-1970s [49]. The original systems were dedicated to head imaging and were very slow. It took hours to acquire the images for each individual slice. The newest scanners collect as many as four slices of data in less than 350 microseconds, therefore decreasing the scan time and reducing the x-ray dose on a patient [49]. Even though improvements have been made CT scanning still is a relatively high-dose procedure. Patients receive a significant dose of radiation, which could harm the health of a patient. In spite of the use of magnetic resonance imaging, with faster CT scanners and helical techniques CT is becoming more common [50].

During some CT scans, contrast agents may be used. A contrast agent is a substance used to highlight an organ or tissue during examination. These agents have the large benefit of producing better images, but they are not without a risk. When injecting a patient with a poor functioning kidney, the

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effect of the contrast media can lead to severe damage to the kidney. This is called contrast nephropathy (CN) and is sometimes irreversible and could lead to death. Hydration is the only option to prevent or reduce chances of CN [51]. The rationale for this approach is that giving fluids before the examination may correct subclinical dehydration, whereas hydration for a period of time afterward may counter an osmotic diuresis (raised urine production) resulting from the contrast [52].

To reduce the risks of inducing a CN in a patient, the eGFR can be determined through blood analysis in the laboratory of the hospital. Such a blood analysis gives a complete image, many blood levels can be determined, but the results can only be determined within 1 hour (emergency) or 24 hours (normal). The most important question is, whether all patients should have their kidney functions tested or only a specific group. This is one of the focus point of the Dutch Safety Management System [20]. To enable faster testing for a larger group, a new technology such as the lab-on-a-chip might offer a solution. One of the restrictive factors is the costs of use. Current lab analysis is reasonably cheap and competing against the lab is difficult.

3.3 General practitioners

The medical practice generally consists of one or more general practitioners who are responsible for diagnosis, medication prescription and the annual audit of development of diabetes Mellitus and kidney function. Besides the GP, one or more doctor's assistants are present, responsible for triage, the follow up and the 3-monthly check-up of the patients. Often a diabetic nurse is present for the fine tuning of the insulin medication and regular check-ups.

All practices followed the current screening frequency guidelines according to the Dutch general practitioner college, which dictates screening once a year. When the GP needs to know the kidney function, they send the patients to the laboratory with a lab form requesting the complete kidney checkup list. Such a lab list contains among others the levels of creatinine, eGFR, micro albuminuria, potassium, sodium. When a patient is diagnosed with decreased kidney function, the standard procedure is to perform a medication check, give lifestyle advice, start blood pressure monitoring, plan the follow-up protocol and if necessary contact a nephrologist.

When asked about the possible improvements in current method of screening, the GPs primary concern is the difficulty of identifying the patients who have a decreased kidney function. Therefore identification of these patients could contribute to a decrease in patients with poor kidney function. When patients are identified, screening could be improved by better adhering to the protocol. Better screening would be possible when there would be a better discrimination between micro-albuminuria and a urinary infection in the urine. Measuring the kidney function with the lab-on-a-chip needs a blood sample instead of a urine sample. The problems with discrimination between kidney dysfunction and infection were solved. In addition to earlier attempts to identify patients with decreased kidney function, through municipal screening, the GPs state that it is important to involve the medical practice, especially when the tests are offered by a private company. Because patients generally only trust their doctor when their health is the issue.

The consensus is that monitoring once a year should be sufficient for screening the kidney function. However the GPs do understand that patients prefer a higher frequency. They would accept an

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increase in screening frequency to twice a year, to meet the patients' wants. A frequency higher than twice a year could not be accepted. The position of GPs is that in theory it is always better to diagnose in an early stage. However related to this disease, a few extra months until diagnosis makes little difference. An exception might be made for the patients who are at a very high risk (co-morbidity or family history). The GPs do agree that screening and monitoring of kidney function should be better embedded in the medical consultation.

The knowledge among all members in relation to lab-on-a-chip technology was very low. Without an exception, all GPs agree that the lab-on-a-chip device should not be implemented at the patients' homes. They especially are afraid for over-testing and false reassurance.

When asked to make an estimation from the point of view of their patients, the GPs expect that patients are willing to accept the new device. The trend is that patients (a.o. Diabetics) are capable of and have a desire to do more themselves. Self-monitoring is becoming more common in the Dutch healthcare system. Examples are blood pressure and insulin monitoring. It will also be of influence that health and mobility are two very important factors in a human life. The expectation is that this device can have a positive influence on mobility and health. The GPs see one particular benefit to patients, the use of a small puncture in the fingertip instead of getting a vena puncture. Especially for patient with poor blood vessels (after chemotherapy or prolonged DM) this would be a major improvement.

The general practitioner is, in the healthcare setting, the responsible caregiver for all chronic diseases. Because the number of patients with a chronic disease is growing, this is contributing to an even higher workload for the GPs. Whether the lab-on-a-chip could improve this problem is questionable. The GPs think that the solution should be found in developing more and smaller practices, or more assistants per practice. The implementation of this device could increase the workload rather than reducing it. With the lab-on-a-chip at the medical practice, an additional test needs to be done instead of outsourcing it to the laboratory.

The costs of purchase and use of the lab-on-a-chip are of great importance to possible implementation. In this particular case, costs could work both in favor of and against the introduction of the lab-on-a-chip. The negative effect on implementation is high costs of the new device. The GPs agree that when the device becomes too expensive or not reimbursed, the lab-on-a-chip will not be bought. A change to the reimbursement system could contribute to a higher uptake of the lab-on-a-chip in primary care. In the current healthcare system there are fixed costs for requesting a kidney function analysis at the lab. If this would change and GPs would have to 'shop' for the best deal, a situation arises that the GPs detest. GPs argue that they would rather purchase the lab-on-a-chip and perform the tests themselves than to negotiate on prices. No certainty on the possibility of this situation can be given, but with the changing healthcare and financial cuts it is a possible situation.

There is one crucial factor related to the uptake of lab-on-a-chip. Those are the parameters and requirements the device should offer. The most important demand is that the device should be a replacement of the lab analysis, not an addition to the current screening. So the lab-on-a-chip should be able to give all the desired serum levels in the blood sample, with high reliability, as currently requested on a lab form. When used in the medical practice, it most likely will be used by the assistant. It is very important that the device is easy to use and maintenance is low. Some additional

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wants are that the device should be small and handy (portable in purse), the chips should be of sufficient sustainability, the device should have a link to the computer system, such that the results do not need to be filled in by hand and finally no more than a monthly calibration should be necessary.

In conclusion, it can be said that the device is not of a clinical addition in the primary care, or more specifically DM care. There is a discrepancy between the acute point of care diagnostics, for which the lab-on-a-chip could be beneficial, and the chronic and long period of developing decreased kidney function among patients with DM. A higher uptake of the lab-on-a-chip can be expected if a population is found with a more acute form of kidney dysfunction. Thus a better match between device and disease.

3.4 Patients

The potential of a novel lab-on-a-chip technology which measures indicators of kidney failure in diabetics was found through a questionnaire among 22 patients with DM type 2. This number is too low to make generalizability possible.

None of the patients interviewed was familiar with the term 'lab-on-a-chip'. Therefore the device was explained and the glucose meter was given as a comparable example. The results of the questionnaire among patients are split into two, starting with the qualitative results.

First, some background characteristics on the population sample. The majority of the patients were in the age-group 50-75. This is equal to the prevalence of diabetes type 2 in the Dutch population. The gender ratio male: female was 13: 9. The age distribution of the years since onset of the disease was one to 20 years. The majority of the patients were not (yet) diagnosed with decreased kidney function.

Patients had a relatively positive judgment on the possibility of self-testing their kidney function with this device. They are unanimous in their statement that the responsibility for treatment and care still lies with the doctor. The GP stays the one who decides what to do next. Therefore a good feedback system of the lab-on-a-chip is very important, both between device and patients as between patient and GP.

The patients see the possible reassurance on the functioning of their kidneys by frequent screening as a positive point of the lab-on-a-chip. However reassurance is one of the points of concern among GPs. The GPs try to prevent over testing and false negative results.

One potential patient population whom prefer this particular type of device are the patients with poor quality of their veins. For instance, in patients with prolonged diabetes or patients who underwent chemotherapy a vena puncture is a painful intervention. A small puncture in the finger, as is required for the lab-on-a-chip, is much more comfortable and less painful compared to a vena puncture.

Not health related, but beneficial for a large group is the time efficiency of the device. A hospital visit is no longer needed, therefore they do not need to take hours off from work. This argument is especially important to the Dutch working population.

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Patients do not know how reliable the results of the lab-on-a-chip are and what the protocol will be in relation to interpreting these results. Some disagreement can be found related to cost and reimbursement. Some patients see this as an important aspect in relation to the use, but the majority states to use the devices despite the need for personal investments. Personal investments and easement of use are two important parameters related to the usefulness of the lab-on-a-chip for kidney dysfunction.

One of the restrictive arguments towards the want for the lab-on-a-chip is the high amount of patients that is comfortable with the current location of the blood analysis. They do not have a problem with visiting the hospital once a year for a blood sample analysis.

A final common result is the low number of demands the patients require from the lab-on-a-chip. The most important requirement of the device is that it should be handy and easy to use. Preferably one button, so that it would be difficult to misuse it.

The research showed that there are two areas where the needs and wants of the patients do not coincide with the current practice. These are the desired frequency on screening and the related option of self-testing versus implementing the lab-on-a-chip at the medical practice. These results are plotted against age and gender, to identify the best location and patient group with the highest preference.

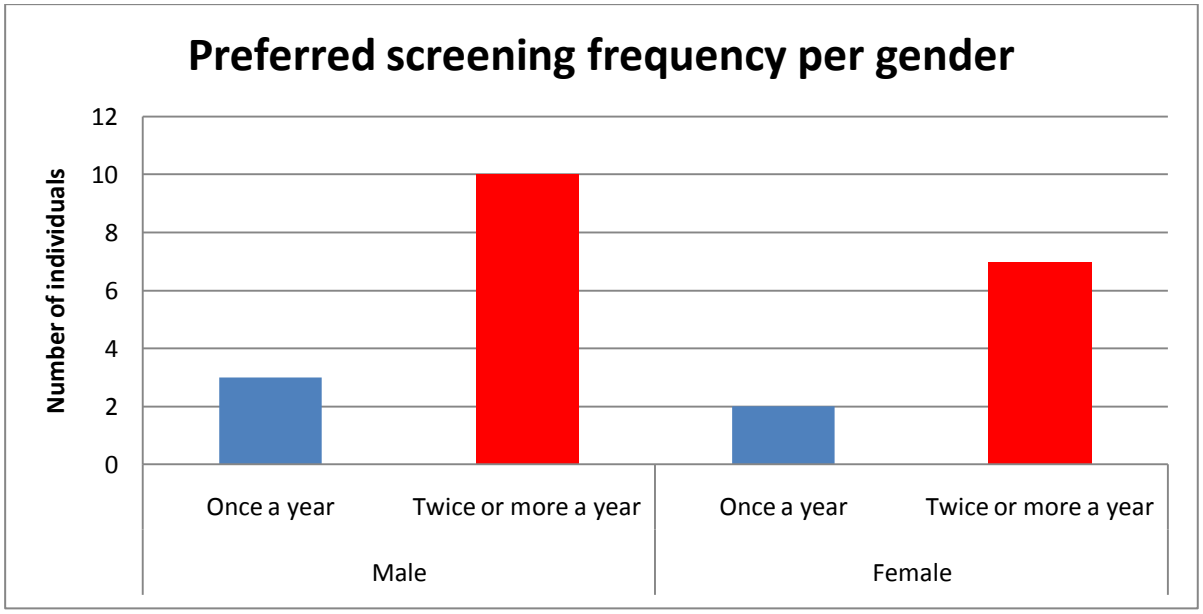

Figure 5 Preferred screening frequency of the kidney per gender. Blue bars represent the current practice, red bars represent a higher frequency

Figure 5 shows the current practice in comparison to the desired higher frequency. In *Appendix 8* the figure is divided in more specific frequencies. The desired frequencies found in figure 5 per gender are that 77% of the male population and 70% of the female population prefers a screening frequency of more than once a year. The desired frequency among patients is higher than the current clinical practice offers. These results are independent of gender.

In figure 6, current practice and higher frequencies are generated per age group.

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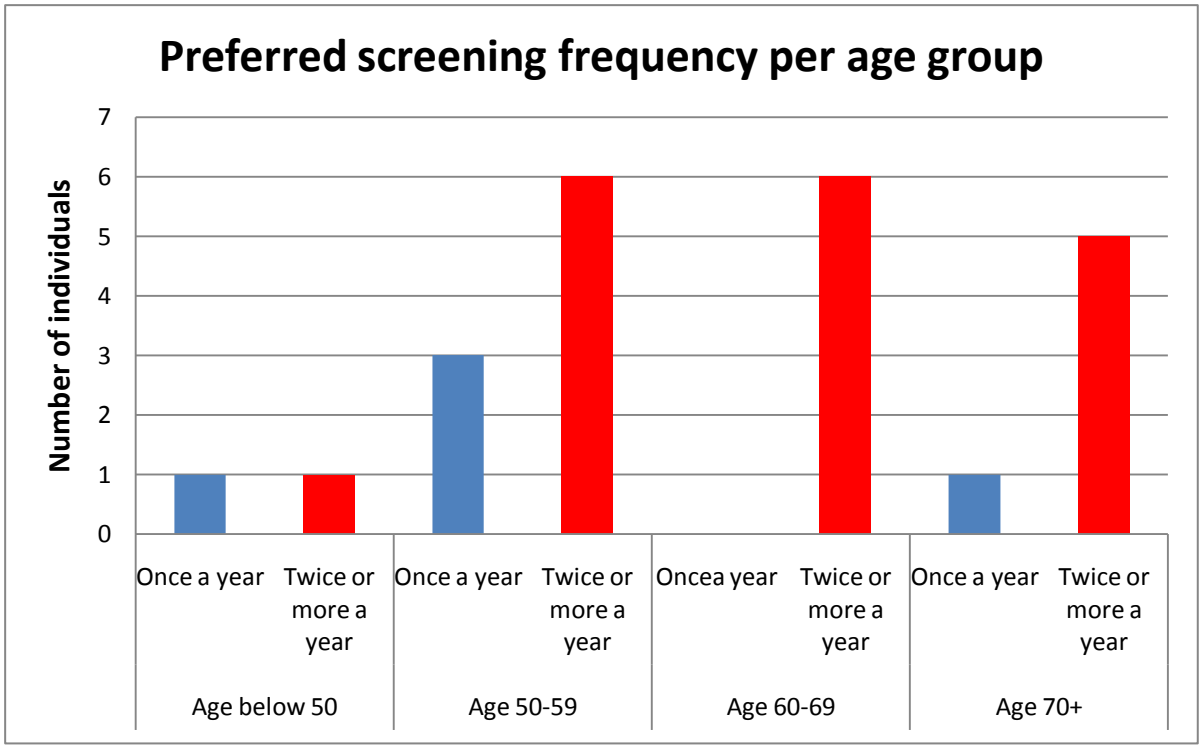

Figure 6 Preferred screening frequency of the kidney per age group. Blue bars represent the current practice, red bars represent a higher frequency

The found desired frequencies preferring a screening frequency of more than once a year is 50% in the age group up until 50, 63% in the age group from 50-59, 100% in the age group from 60-69 and 83% in the age group 70+.

These results suggest that there are differences in preferences. Especially the elderly prefer a higher screening frequency, which might be explained by the progression of the disease. Especially the patients with a prolonged state of DM have a high chance of development of kidney dysfunction. When risks are higher, or when a decreasing kidney function is determined, a higher need for more frequent screening occurs. In *Appendix 8* the figure is divided in 5 years of age intervals.

The interviews suggest that besides the frequency, the location of use of the lab-on-a-chip is of importance to the patients. The lab-on-a-chip could be implemented in the current medical practice and then used by the general practitioner or the assistant. The other option is to use the lab-on-a-chip as a self-testing device, thus use it at the patient's homes. The results are plotted per gender in figure 7 and per age group in figure 8.

The patients seemed to disagree with the notice of the GP that self testing is not a good idea.

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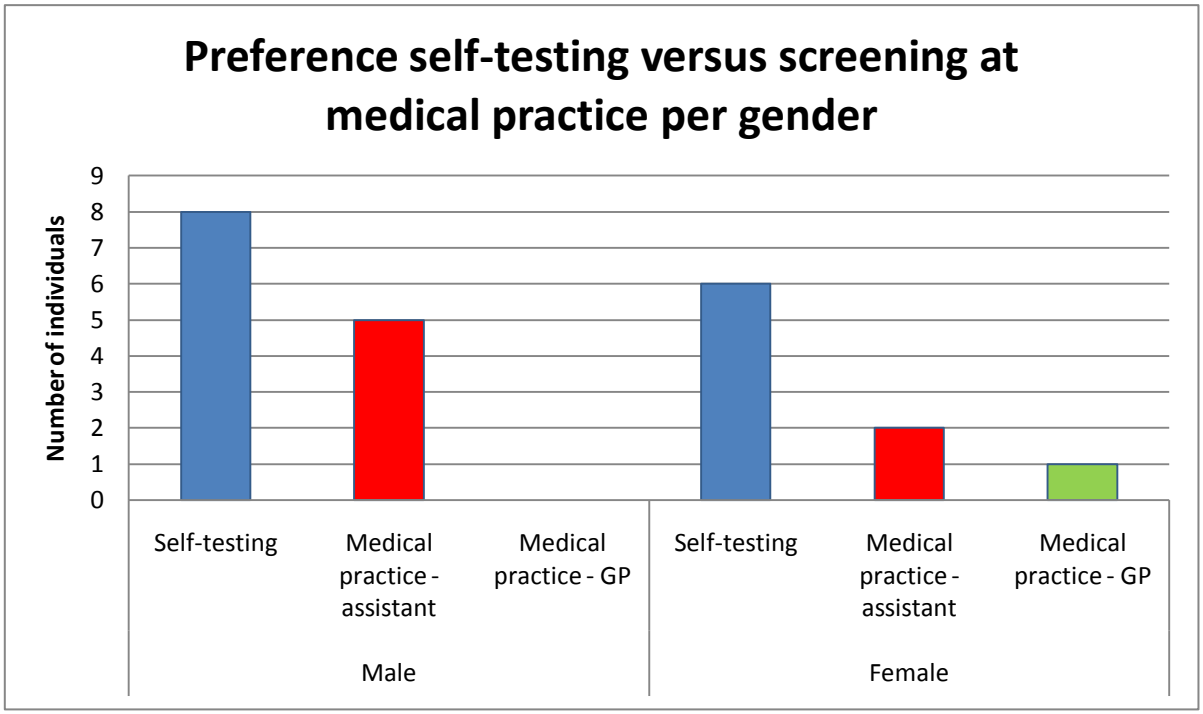

Figure 7 Location of choice per gender. The blue bar represents self-testing, the red bars reflects testing at the medical practice by the doctors assistant and the green bar represents the preference on testing at the medical practice by the GP

Figure 7 shows that 62% of the male and 67% of the female population prefers the option of self-testing. The found results show that, even though one in three patients prefers testing at the medical practice, the majority of the population sample has a preference towards self-testing. There does not seem to be a gender difference. When the same variable, the location of the test, was plotted against age instead of gender, there does seem to be a noticeable difference in preference towards self-testing.

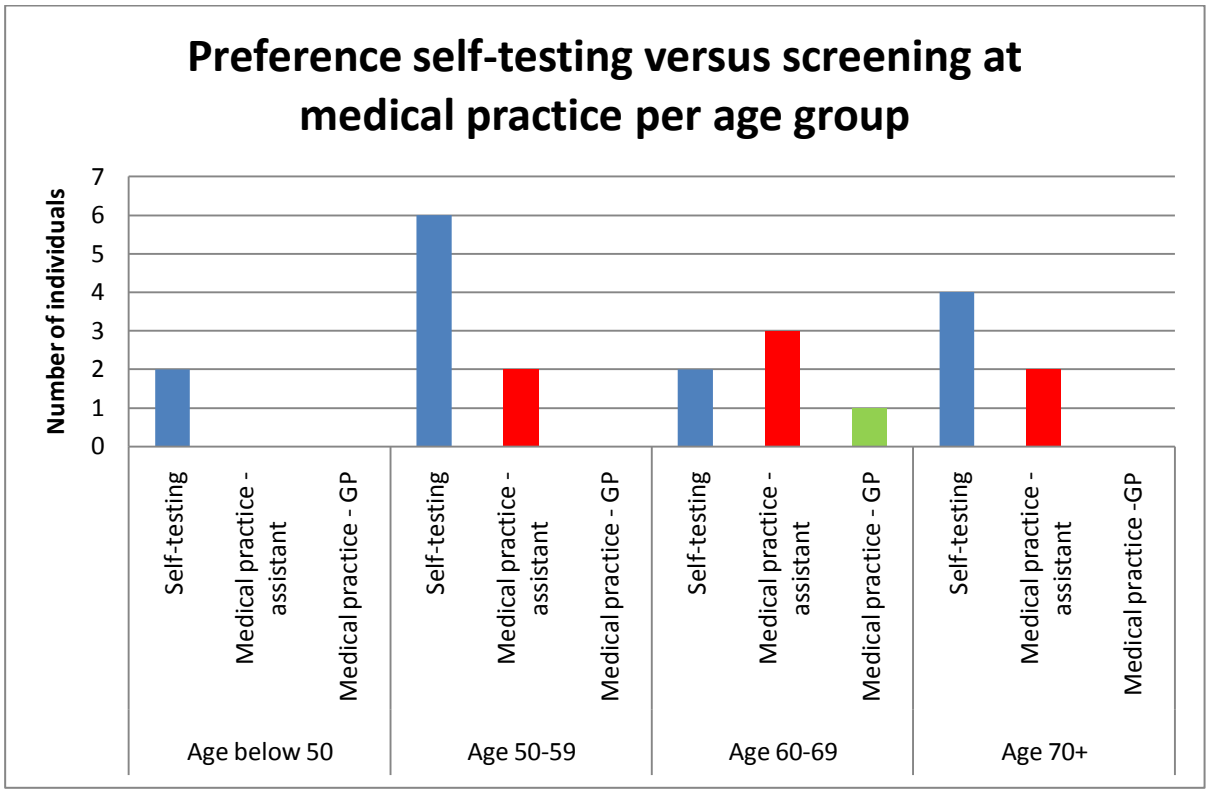

Figure 8 Location of choice per age group. The blue bar represents self-testing, the red bars reflects testing at the medical practice by the doctors assistant and the green bar represents the preference on testing at the medical practice by the GP

The option of self-testing is preferred in 100% of the patients in the age group up until 50 years old, 75% in the age group from 50-59, 33% in the age group from 60-69 years and 67% in the patient population of 70 years and older.

Especially the younger groups prefer self-testing. It might be that they grew up in an electronic era, so they are more familiar with electronic devices. It might also have to do with their daily schedule. Having a self-test means that they do not have to visit the hospital, so no absence at work. Interesting is the high number of patients in the 70+ group that prefer the self-test. Usually the elderly are seen as the population who are unwilling to work with electronic devices. In *Appendix 8* the figure is divided in 5 years of age intervals.

Overall there seems to be no need among patients to let the test be done by the GP. This is consistent with current treatment. Because screening and monitoring of patients with diabetes Mellitus is currently performed by the assistant.

3.5 Radiology

This part of the research answers the question what the potential is of a novel lab-on-a-chip technology, which measures indicators of kidney dysfunction in patients who are in need of a CT contrast scan. The research gave information about the current protocol on contrast scans, the need to improve screening on decreased kidney function in all patients before a contrast scan and the perceived benefits of the lab-on-a-chip technology. The results are found through the earlier mentioned interviews among 11 specialists and a preliminary market research which had 4 participating hospitals with 42 specialists. In this order the results will be discussed.

Between specialists with regard to the following points, there was a consensus. Despite all the new protocols and systems, there is still room for improvement of the incidence of contrast nephropathies. The percentage of patients with contrast nephropathy (CN) after a scan is not yet reduced to 0%. Because of the large negative health effects when CN does occur, the overall opinion is that improvements are needed.

In relation to the planning and protocol on an organizational level, there are some possible improvements. These changes could be beneficial to both the hospital and the patients. The current roadmap for patients who need a contrast scan according to the requesting clinic is as follows. The patient receives the lab form from their doctor and walks to the laboratory department. After blood has been drawn through a vena puncture, the patient goes to the radiology department to set an appointment and then goes home. If the lab-results show no abnormalities, the patient will have the procedure as planned. However if abnormalities in the serum levels are found, the patient will have to return to the hospital, a protocol on hydration has to be made and the appointment needs to be adjusted. This is very time consuming, both for the patient as for the hospital. Introducing the lab on a chip, which makes a faster GFR determination possible, would be beneficial. Blood results are known before the patient sets their appointment and no extra hospital visits are necessary.

The idea of a lab-on-a-chip, which only needs a small blood sample collected from the finger tip, instead of a vena puncture, is seen as a very positive point by the radiographers and radiologists. The lab-on-a-chip is both more time efficient and more patient friendly than drawing blood through vena puncture. This is especially the case with patients that have a poor quality of the blood vessels. This

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device will always be more patient friendly, the only point of attention is habituation. When the lab-on-a-chip is introduced to the medical practice, this will be known as standard practice. Only patients who are familiar with the earlier treatment will notice the improvement on comfort.

There are some differences between hospitals with regard to screening the kidney function of patients before a contrast scan. These differences are somewhat leveled in the last years since the Safety Management System (SMS) was introduced. There are two main strategies in the Dutch hospitals. First is following the SMS guidelines where all high risk patients get a GFR determination before a contrast scan is performed. The other option is to alter their protocol and screen all patients for whom a contrast scan is requested. The first option even though it means less work, has some limitations. Not all high risk patients (peripheral arterial disease, heart failure, age > 75 years, anemia, symptomatic hypotension, contrast volume >150ml, diuretic and nephrotoxic drugs) are identified as high risk patients. Therefore it is possible to miss undiagnosed high risk patients and give them contrast media without hydration. Screening all patients who need a contrast scan makes sure that no patients with a decreased kidney function are missed, thus the number of CN will be reduced. Specialists indicate that the extra work that arises is not the main problem when a hospital changes the strategy. The main problem is the lacking awareness of the incidence and severity of the disease. Because of the high interaction between departments in a hospital, other professions should be aware of the need to reduce the incidence of CN in patients.

When implementing a new technology the costs are always of great importance to the possibility of success. The specialists were asked their opinion on importance of equal cost of the lab-on-a-chip in comparison to analysis in the lab. Also the effect on possible implementation when the costs turn out to be higher than the current practice is determined. The answers were variable; some indicate that in the current healthcare system, costs is the most important factor, thus equal costs should be the minimum. Others pointed out that when the hospital has a focus on 'planetree' treatment (*human-centered care in a healing environment)*, a device that gives less discomfort should be introduced despite a higher price. These different opinions depend on the position of the specialist. When they take place in a financial committee their answers are given with more assurance of accuracy.

The most important disadvantage in relation to the implementation of the new lab-on-a-chip device would be the inability to test more than the GFR. Even though the radiology department is only interested in the GFR, in favor of other departments, other levels are tested at the same time. It would be beneficial for the easiness of implementation when the lab-on-a-chip would be able to test more substances in the future.

The interviews indicated a degree of dispersion on the best location for positioning and use within the hospital and which patient population could benefit the most from treatment with the lab-on-a-chip. It is important to realize that these benefits are not purely health related! The scenario analysis was conducted among 42 radiologists and radiographers from four different hospitals. The information gained during the interviews resulted in the following scenarios.

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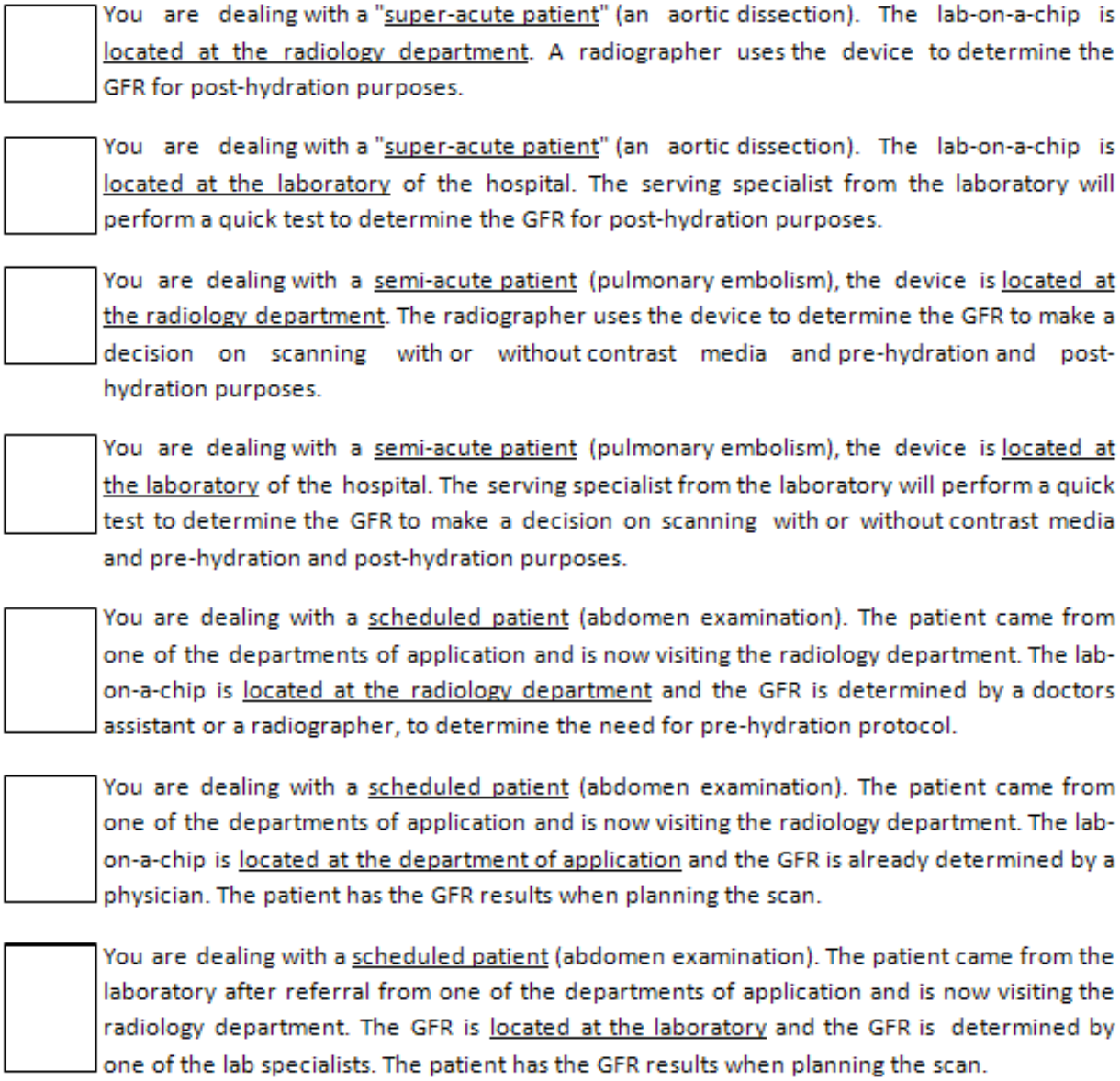

Figure 9 Overview of scenarios. Original form (Dutch) in Appendix 6

The population is divided in acute, semi-acute and scheduled patients. The difference between these sub-populations can be found in time-line until treatment and perceived benefits. There is a large range of locations where the lab-on-a-chip could be used, these location are grouped into three options, the radiology (location of the CT scan), laboratory (current location of blood analysis) or the department of application (all other departments in the hospital). The results when all hospitals are compared show the distribution of importance levels between location and population preference as shown in table 2.

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Table 2 Importance levels of location and population with corresponding 95% CI.

Location of the hospital		Importance population	Importance location
Leiderdorp N=19	**Mean (SD)**	55.7 (19.0)	44.3 (19.0)
Doetinchem N=7	**Mean (SD)**	52.7 (16.4)	47.3 (16.4)
Harderwijk N=9	**Mean (SD)**	49.6* (13.9)	50.4* (13.9)
Hengelo N=7	**Mean (SD)**	75.3* (18.4)	24.7* (18.4)
Total N=42	**Mean (SD)**	57.2 (18.9)	42.8 (18.9)

95% Confidence interval of the difference (Total) Std. error of mean is 2.9	Upper limit	Lower limit
Population	63.1	51.3
Location	48.7	36.9

With an average importance level of 57.2%, the specialists see the patient population as more important than location in relation to implementing the lab-on-a-chip. The mean differs from 49.6%, which represent a negative preference towards population, until 75.3% which represent a large positive preference on population. The 95% CI show that the hospitals Hengelo and Harderwijk have levels significantly different from the total mean. Respectively have a more positive importance level of lab-on-a-chip on population and more negative importance level on population.

When looking at the location, it is clear that in three out of four hospitals the importance level of location is inferior to the importance levels of the population. With a mean from 24.7% to 50.4% the importance levels of the location are lower than the importance level of the population. As can be expected, the 95% CI of the hospitals in Harderwijk and Hengelo are significantly different from the total mean.

The difference between the hospitals in Hengelo en Harderwijk is remarkable. The hospital in Harderwijk is the only hospital with a (very small) preference to the location, whereas employees of the hospital in Hengelo elect the patient population. This difference can be explained by the answers given to the last question of the preliminary market research. The radiographers and radiologist were asked what would be the most important reason to implement lab-on-a-chip screening in the protocols for contrast scans. The answers were very diverse. Some indicated time as most essential, others wanted to reduces the number of CN and a third group chose the option 'otherwise' and filled in their opinion by hand. The radiographers and radiologist from the hospital Hengelo choose the option time efficiency and 'otherwise'. In Harderwijk the radiographers negotiate and gave one general answer, which were CN reduction in semi-acute patients and time efficiency for scheduled patients. The radiographers in Doetinchem were not willing to answer this question.

In figure 10, the results of the combination of location and population are plotted. The high bars equal a better result. The 95% confidence intervals are determined per scenario. The black lines represent the upper and lower limit of thee 95% confidence interval. The results seem to indicate

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that the semi-acute and planned patients are the populations of preference, they were granted more points by the radiographers and radiologists.

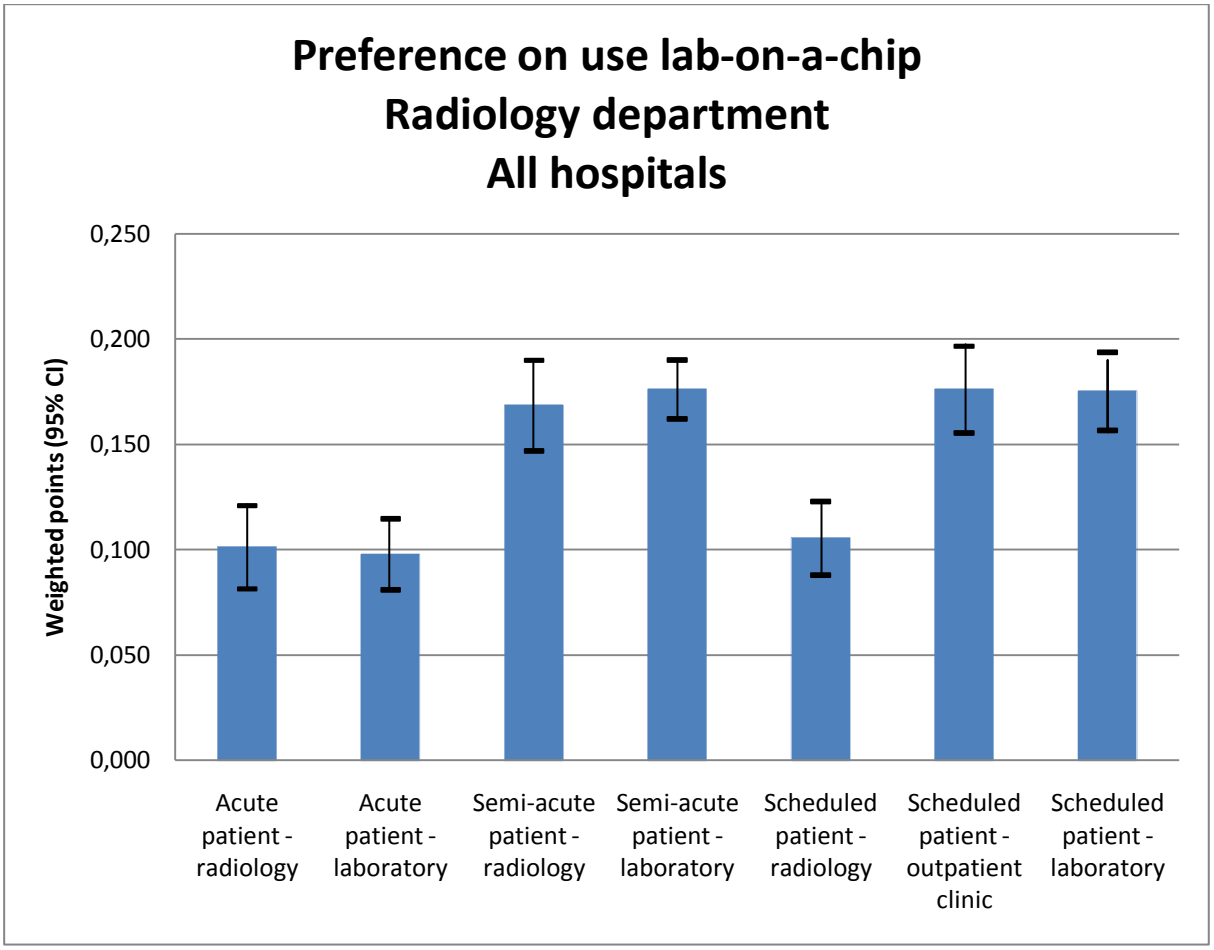

Figure 10 Prefences on combined location and population per hospital with 95% confidence interval

The bars related to semi-acute and scheduled patients are almost two times the size of the bar for acute patients. They also have 95% confidence levels that represent a significant difference between the acute patients and the other patients. Therefore it can be said that there is an overall aversion towards the use of the lab-on-a-chip independent of the location on acute patients. This can be explained by the simple reason that acute patients always get a contrast scan. The benefits of performing the scan will always outweigh the possible disadvantages. The example of patients with an aorta dissection is given. These patients need diagnosis very fast followed by immediate surgery. The possible effects on kidney dysfunction are inferior to the changes of death by the aorta dissection.

The third bar that is a significantly different is the bar that represents the scenario of screening scheduled patients at the radiology department. The height of the bar and the confidence levels are comparable with the results of the acute patients. Both professions (radiologists and radiographers) are skeptic towards this possibility of use of the lab-on-a-chip. They wonder who gets the responsibility, how it will affect the workflow and whether training is necessary.

When eliminating the acute patients, there does seem to be a slight preference towards implementation of the lab-on-a-chip in the laboratory of the hospital. This preference however is not

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significant. Reasons given for the preference towards the laboratory are the expertise present at the laboratory and the minor effect on workflow. When the laboratory is located near the radiology department, there would be no benefits for screening at the radiology department, both for staff and patients.

The results are also determined per hospital. The 95% confidence intervals are presented, to demonstrate the high difference among but also within the hospital. A short explanation of the results per hospital will be given.

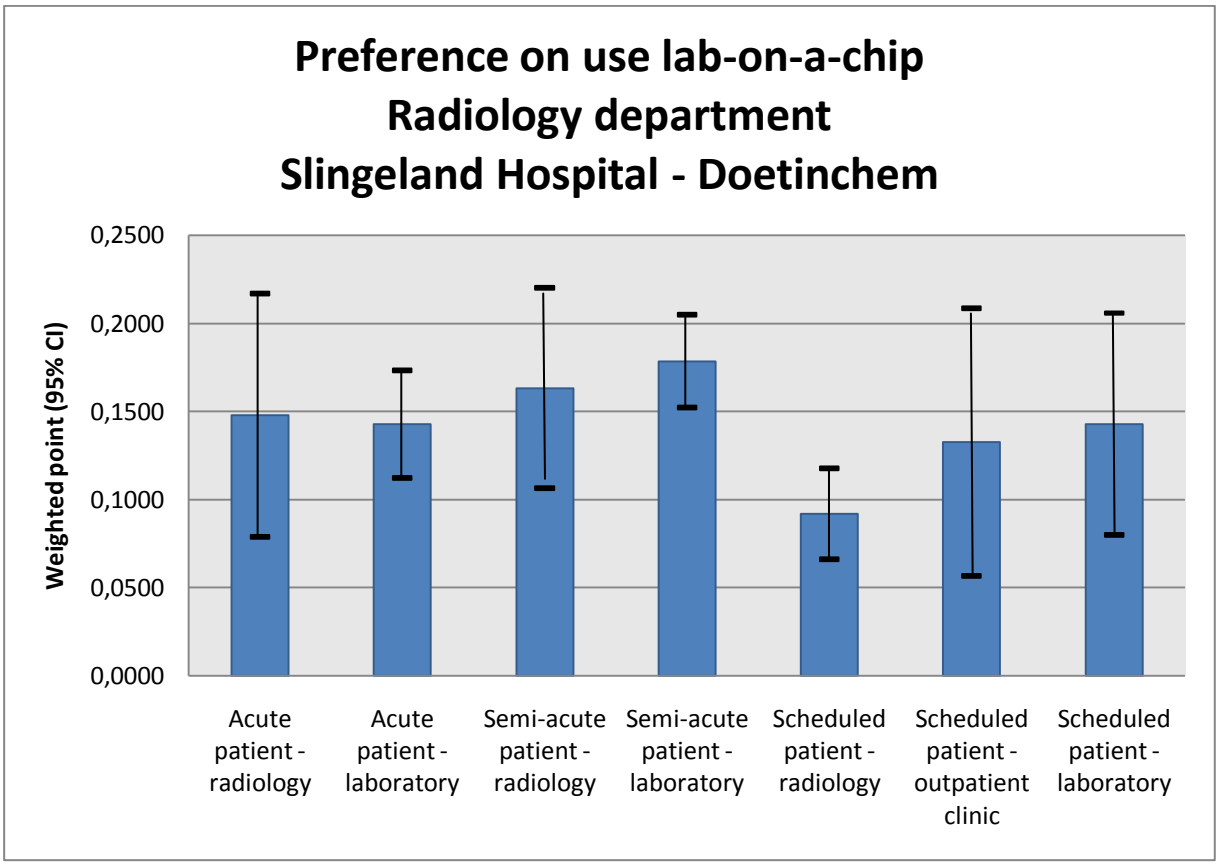

Figure 11 Preference use lab-on-a-chip - Slingeland Hospital

The first hospitals results are from the Slingeland hospital in Doetinchem, the results are shown in figure 11. The results of the scenario analysis in Slingeland Hospital, show less clear results when compared to the total results. The 95% confidence intervals of the scenarios are overlapping. Therefore there is no significant difference between the scenarios at the Slingeland Hospitals. The intervals of the scenarios acute/laboratory, semi-acute/lab and scheduled/radiology have smaller confidence intervals than the other four. There seems to be more agreement on position in ranking these three scenarios. In the results it is clear that the scenario were scheduled patients are screened at the radiology is ranked seventh. Thus represents the most disliked scenario.

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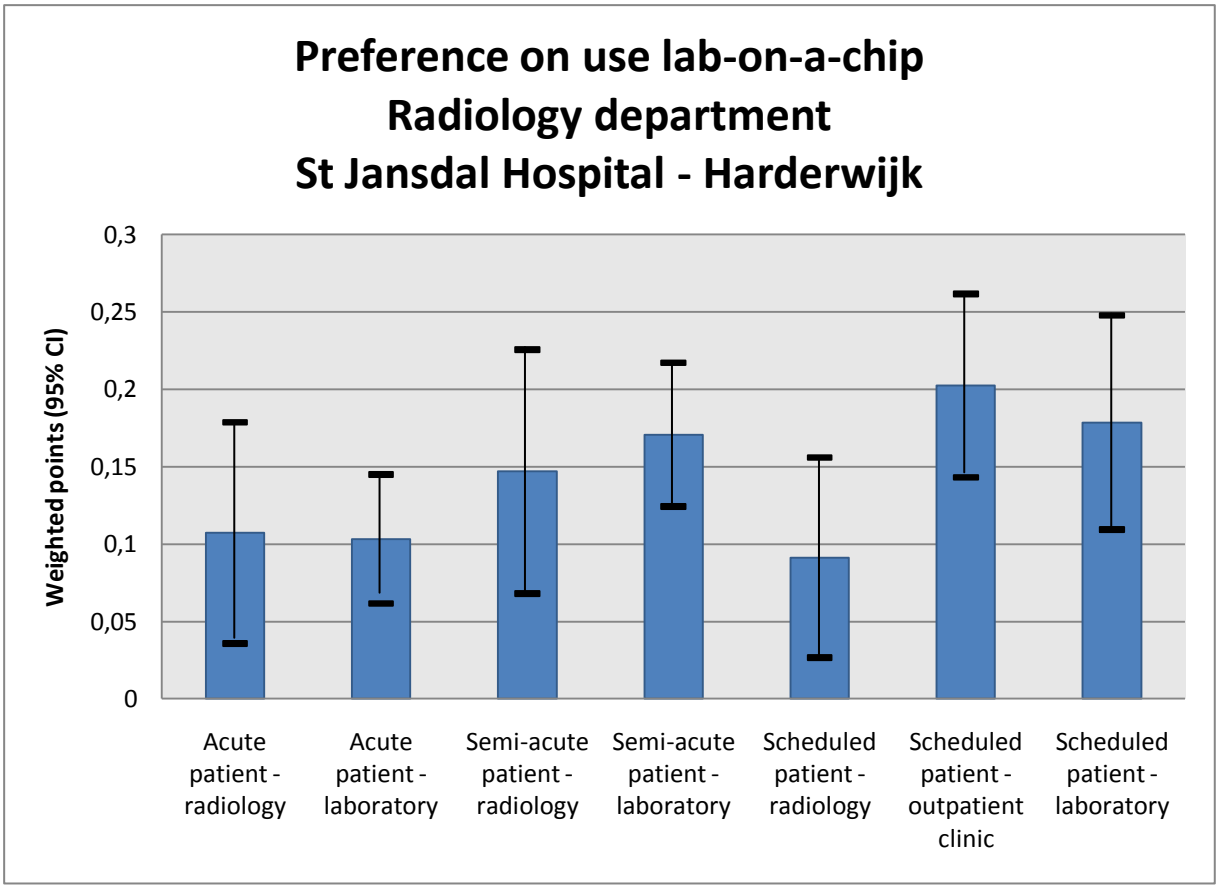

Figure 12 Preference use lab-on-a-chip St Jansdal Hospital

The second hospital, from which the results are plotted in figure 12, is St Jansdal hospital in Harderwijk. The results of scenario analysis among radiographers and radiologists in St Jansdal hospital also show no scenarios with results significantly different from the others. The 95% confidence intervals are all overlapping. There also are no clear smaller or wider intervals at specific scenarios. Even though no significant results are found, the heights of the bars do represent a dislike towards acute patients and the combination scheduled/radiology.

The scenario analysis generated the clearest results at the Hospital Zorggroep Twente (Hengelo). Figure 13 shows that there is a very high and strong aversion among the radiologist and radiographers to the scenarios of use of the lab-on-a-chip on acute patients. The 95% confidence levels are very small, representing a high degree of agreement among the specialists. The other five scenarios have overlap in the 95% confidence intervals, however the intervals are smaller than the intervals in the other hospitals. The major difference in relation to the total results is the non-significant difference of the scheduled patients at the radiology department in relation to the department of application and the laboratory.

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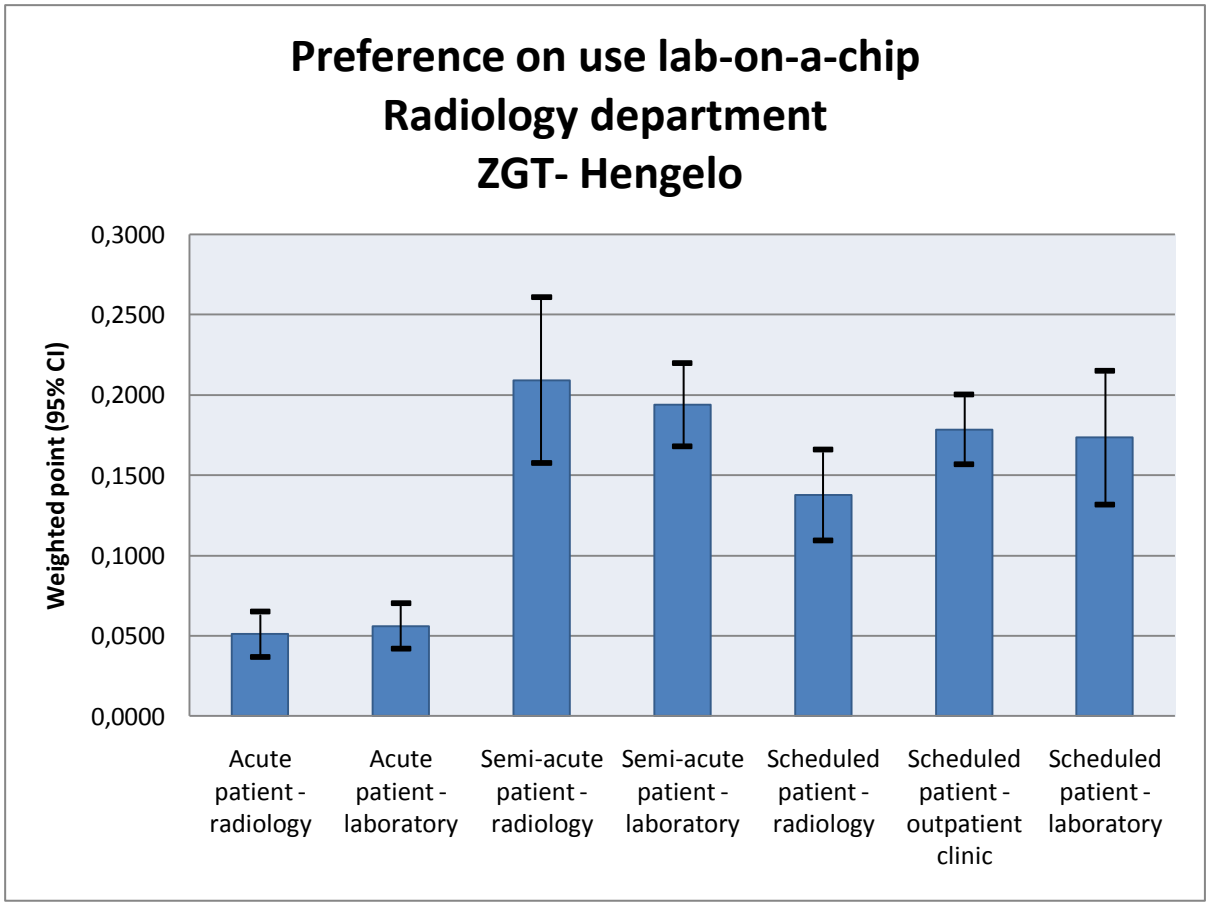

Figure 13 Preference use lab-on-a-chip Zorggroep Twente

The last hospitals from which the radiographers and radiologist were willing to participate was Rijnland Hospital (Leiderdorp). The results from this analysis are displayed in figure 14. The participation grade was higher in this hospital, as a result, the confidence intervals will be narrower. The results related to the acute patients show, equal to the results in Hengelo and the total, an aversion to the use of the lab-on-a-chip. The results of the scenario where scheduled patient are screened at the radiology department are significantly different from the other two scenarios related to scheduled patients. Not significantly detectible, but determined by the height of the bars, is the higher preference towards screening at the laboratory that the specialists in hospital seem to have a. When asked for a reason, the location of the laboratory in the hospital is given. The laboratory is located opposite to the laboratory. When located this near to the radiology department, no advantages for screening at the radiology department are found.

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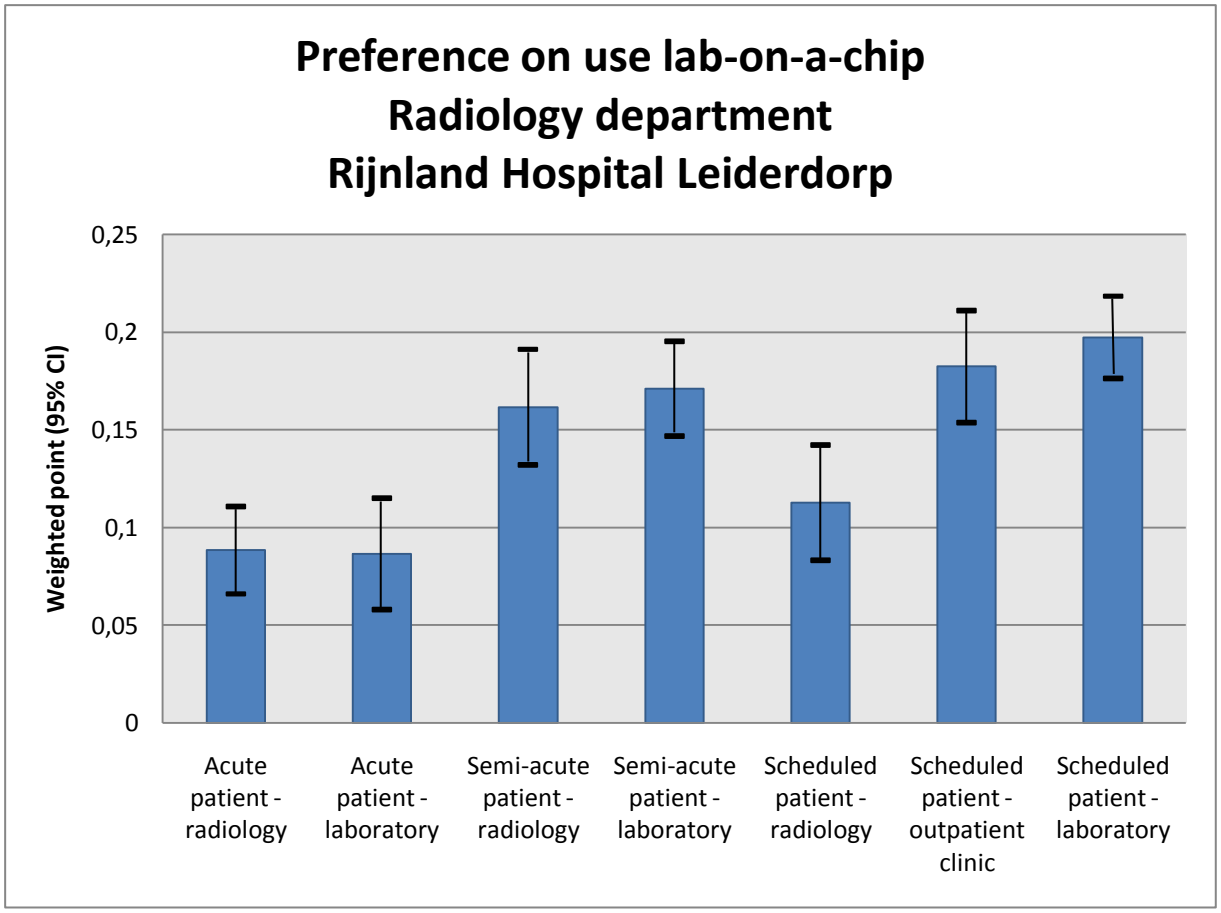

Figure 14 Preference use lab-on-a-chip Rijnland Hospital

The large differences between the hospitals indicate a difficult generalizability. Whether the differences are a result of the composition radiographer-radiologist, size of the hospital, case-mix of the patients or other influences cannot be concluded from these results.

The difference in results within the population and location are determined by ranking analysis and captured in a table. This time the mean values and the standard deviation of the utilities are determined. Per population (table 3) and location (table 4) the three possibilities and their utilities are given.

Table 3 Utilities per population

Location of the hospital		Utility acute patients	Utility semi-acute patients	Utility scheduled patients
Leiderdorp N=19	**Mean (SD)**	2.3 (1.3)	4.6 (1.2)	4.7 (1.2)
Doetinchem N=7	**Mean (SD)**	4.1 (1.7)	4.8 (1.2)	3.4 (1.6)
Harderwijk N=9	**Mean (SD)**	2.8 (1.2)	4.0 (1.2)	4.8 (0.9)
Hengelo N=7	**Mean (SD)**	1.9 (1.1)	5.6 (1.4)	4.3 (1.4)
Total N=42	**Mean (SD)**	2.7 (1.5)	4.7 (1.3)	4.5 (1.3)

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Table 4 Utilities per location

Location of the hospital		Utility laboratory	Utility radiology	Utility outpatient clinic
Leiderdorp N=19	**Mean (SD)**	4.1 (0.8)	3.4 (0.9)	5.5 (1.3)
Doetinchem N=7	**Mean (SD)**	4.2 (0.9)	3.8 (1.3)	4.0 (2.4)
Harderwijk N=9	**Mean (SD)**	4.2 (0.9)	3.3 (0.9)	5.4 (1.6)
Hengelo N=7	**Mean (SD)**	4.1 (0.2)	3.7 (0.5	4.7 (1.8)
Total N=42	**Mean (SD)**	4.1 (0.7)	3.5 (0.9)	5.1 (1.7)

It is important to realize that these values are not independent. It is clear that, with hospital Doetinchem as an exception, the acute patients are not seen as the beneficial population for the use of a lab-on-a-chip. This is corresponding to the figures plotted. The utilities of the semi-acute and scheduled patients are much higher than the utilities of the acute patients, but there is no overall preference. Two hospitals have a higher utility on semi-acute patients and two on scheduled patients. These results are also reflected in the plotted figures. Semi-acute and scheduled patients are both represented by an almost equally large bar.

The radiology department gets the lowest utility values and is the least favorable location to implement the lab-on-a-chip. The value of the outpatient clinic utility is in three out of four hospitals the highest. This would mean that this is the location of choice. The figure (combination of all hospitals) however shows a slight preference for implementation on the laboratory. A decrease in the utilities of the outpatient clinic would be necessary to level the utility values in table 4 to the size of the bars in figure 10. As will be discussed in the chapter 'Discussion', the high utility values of the outpatient clinic might be overestimated because the option outpatient clinic was only offered in one of the seven scenarios.

The utilities show an overall low value for implementation at the radiology department. However, these utilities cannot demonstrate the large aversion towards the specific scenario of scheduled patients and testing at the radiology department. This can be explained because the utilities are individual values and not utility values for the combinations of location and population. Figure 10 does give these combinations, therefore the plotted bars in the figure are a necessary addition to the results.

The radiologists and radiographers were asked to estimate the benefits for the hospital and the patient in relation to the scenario they choose as most relevant patient population and location. First, the accuracy of the estimations was checked by a question on prevalence of CN. The given answers were similar to the prevalence found in the literature. For the best liked scenarios, the semi-acute and planned patients, a choice model was generated. The tree in figure 15 is developed for the semi-acute patients with costs as outcome. The trees per population (semi-acute and scheduled), reflecting all health and efficiency outcomes (costs, discomfort and time) can be found in A*ppendix 9.*

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Incidence level CN

Introducing the lab-on-a-chip gives a minor decrease in the total percentage of contrast nephropathies (CN). The incidence of 3% is an average found in the literature [53, 54]. However no proper research has been done on this subject and incidences fluctuate. Specialists from the radiology department indicated a suspected decrease of CN for semi-acute patients from 3% on average for the whole population to 2%. The incidence for scheduled patients depends strongly on the protocol the hospital works with. When following the SMS guidelines, thus only screening the high risk patients, the lab-on-a-chip might be able to reduce the incidence of CN. For hospitals who work with a protocol that dictates to screen all patients who need a contrast scan, a decrease close to 0% of CN will be attained and the lab-on-a-chip does not have a direct health effect.

As a result of CN a patient could die, become healthy again, or need health support through dialysis or transplantation. Contrast nephropathy is becoming more important in the last decades by two reasons. First there is more attention to the disease and secondly, there is a higher incidence because of more CT contrast scans. Adequate numbers on incidence of CN and related outcomes (death, health, and dialysis) are missing. The literature describes some prevalence's, the ratios in the tree in figure 15 and *Appendix 9* are based on these numbers. Almost one out of four patients who developed contrast nephropathy dies because of the consequences. Over 75% of cases of nephropathy following angiography are reversible. However, up to 10% of the cases are more severe, requiring dialysis support [55]. The chances of getting kidney transplantation are very small.

Costs

The possible cost savings of society for semi-acute patients are calculated by using the incidence numbers related to pulmonary embolism. Pulmonary embolism was the example related to semi-acute patients. In the Netherlands the incidence is 2-3 per 1000 inhabitants (per year), thus 33.000-50.000 patients per year [56]. The number of scheduled patients is not exactly known, but the total number of contrast scans is estimated to be 0.5-1 million scans per year [57]. In this study the number of scheduled patients is set at 500.000 patients per year.

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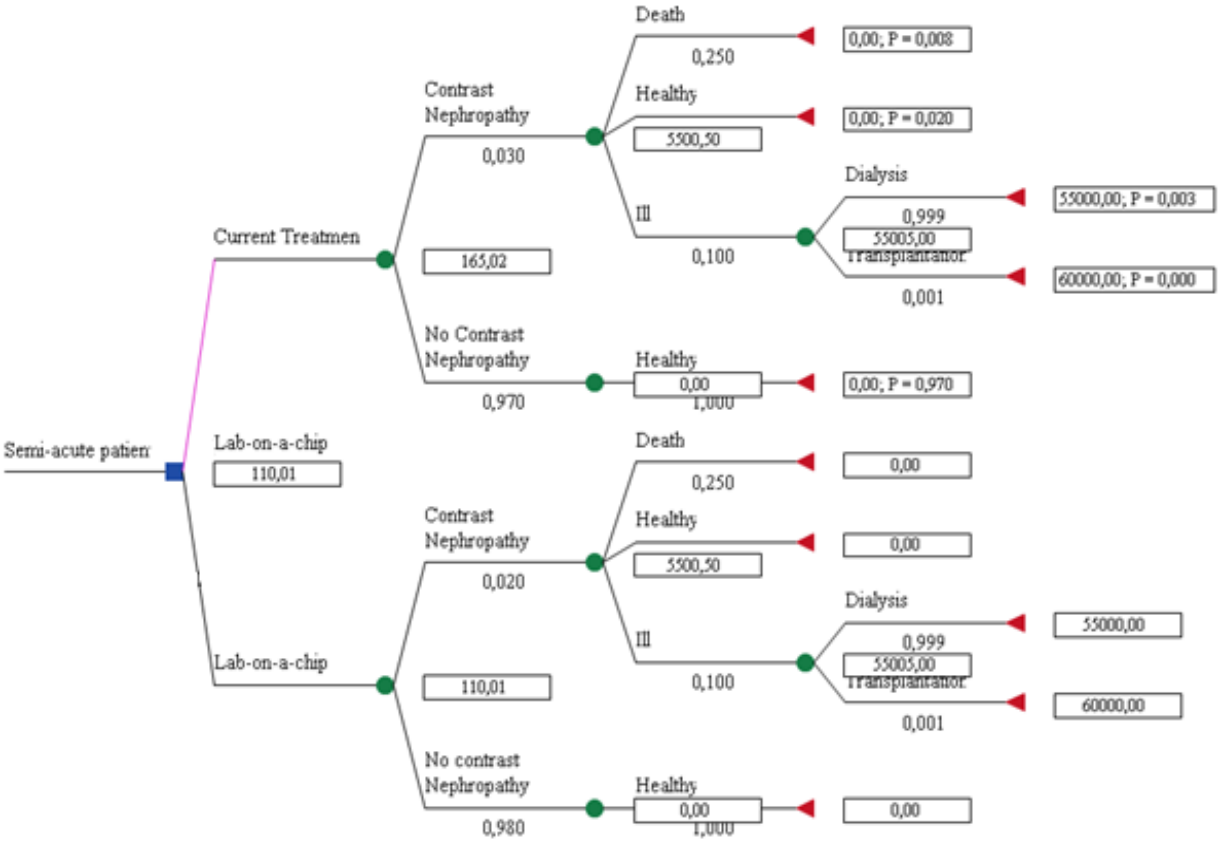

Figure 15 Healthcare tree related to the semi-acute patient and cost efficiency

The values, which are used, are adopted from the literature. Costs for healthy or deceased patients are set at € 0. The costs for transplantation are € 60.000 per patient with an additional € 10.000 per year per patient. Costs of dialysis are approximately € 50.000 to € 60.000 per year per patient [58]. When relating the costs to the incidence of contrast nephropathy, the semi-acute patients is the population with the highest possible cost savings. Related to the protocol hospitals use, the saving by scheduled patients can be large or only marginal. It might even occur, when the costs of a lab-on-a-chip are higher than the current lab analysis, that there will be loss of money.

When introducing the numbers into the tree, the following results are found. The costs per patient per year without lab-on-a-chip are €165. When introducing the lab-on-a-chip and reducing the incidence of contrast nephropathy, the costs per patient per year are €110. When relating these costs to the number of patients the following costs are found.

Table 5 Possible cost savings on reduction contrast nephropathy

	Semi-acute (pulmonary embolism)	Scheduled (total)
Current situation	€ 5.4-8.3 million	€ 550- 825million
Lab-on-a-chip	€ 3.6-5.5 million	€ 550 million

This would mean possible cost savings of €1.8 - € 2.8 million per year for semi-acute patients. For the scheduled patients the costs saving can be as low as €0 per year, up till €275 million a year. However these savings are purely the possible costs savings when reducing the incidence of patients with contrast nephropathy. Costs related to purchase and use of the device are not taken into account.

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The numbers do show the possibility of cost savings in the semi-acute population (for the patients sample population of pulmonary embolism). When the lab-on-a-chip is further developed and more accuracy on costs can be given further analysis should be performed to weigh costs versus benefits.

Discomfort

The intervention will change from a vena puncture to a small puncture in the fingertip, this is regarded as a mild decrease in discomfort.

The same analysis tree has been used, but now with decreased discomfort, compared to the current standard, as outcome measure. Even though the two populations, the smaller semi-acute and larger scheduled group, experience the same reduction in discomfort, when related to their total discomfort the reduction will not be experienced as equal. The discomfort that the semi-acute group has to deal with during the rest of their treatment will be much higher than the reduction in discomfort gained by the change from vena puncture to a finger blood sample.

The scheduled group will experience the largest decrease in discomfort. However, as said in the qualitative analysis, this decreased discomfort will only be noticed by the patients who can compare new versus old treatment. To the other patients it will be perceived as standard, not improved, care.

Time efficiency

Finally, the time efficiency is also taken as an outcome. The results from the preliminary market research show that there is an expected difference between the time efficiency for the patients and the hospitals. They major influence in time efficiency is the current protocol and the population, semi-acute or scheduled.

- When considering the scheduled patients, the patient's time efficiency is estimated to be variable. When the lab-results of the patients are negative, (good kidney function) the maximal time efficiency is estimated at one hour. However, when a positive outcome is found (poor kidney function) the time-efficiency can be as high as one day. With the new device, patients can be sure that the scheduled scan time is accurate, no information is missing and no extra hospital visits are acquired.
- The time efficiency for the hospital is smaller. The estimation on hospital time efficiency for scheduled patients is five minutes. Time efficiency can only be gathered by a reduction in the number of canceled scans and decreasing the number of phone calls to colleagues to find missing patient information.

The efficiencies related to the semi-acute patients are otherwise distributed. Because of the nature of the disease, the time efficiency is equal for patient and hospital. The preliminary market results show an efficiency of one hour.

- The identification of the effect on positive time efficiency for the patients is not yet clear. One hour less in the hospital will not make an important time efficient change to them. A health improvement because of an hour saved in timed will be the gained outcome by time efficiency.

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- For a hospital, one hour less waiting time means the possibility of immediate scanning. A patient who stays an hour less in the emergency care is very beneficial, because beds in emergency care are very expensive.

A final result, with a reflection to future health settings, is the unanimous opinion of the radiologists and radiographer on 'walk-in' contrast scans. The principal of walk-in scans means that, patients who are in need of a scan come to the radiology department at a moment of their choice. The radiographers and radiologists think that scanning according to the walk-in principals is hard to accomplish, with or without the lab-on-a-chip. Some hospitals tried this system for more easy scans, such as X-ray or simple CT scan, but it is not an effective way of working yet. Especially for contrast scans that need contrast media introduced prior to the scan, extra time and staff is necessary. This time and staff is not at all times available, but should be when offering contrast CT scans on a walk-in schedule. The advice is to not make this one of the focus points of implementation attempts.

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4 Discussion

4.1 General

Because of the wide scope of this research and the multiple methodologies applied, the points of discussion will be presented per focus point. The idea of using a lab-on-a-chip for point-of-care measurements of the kidney function is not entirely new. In the United States, such a device is in development as well. However, the technology that is used in this lab-on-a-chip measuring creatinine levels in blood is one of a kind. The methodology of using capillary electrophoresis is unique. The company needs to remain to this technology to survive in the development market.

The primary limitation in this research was the wide field of possible implementation areas that could be investigated. The focus was on the largest population size within the population with kidney dysfunction (diabetes Mellitus and contrast nephropathy) in each of the three branches, the self-care, primary care and hospital care. Even though the literature review suggested diabetes Mellitus and contrast nephropathy as most relevant on the areas in terms of population's size and familiarity to self-monitoring, more research should indicate what the real possibilities on implementation are.

4.2 Self-testing

In total 22 patients with diabetes Mellitus participated in the questionnaire study. The main results were a high preference on more frequent screening and the possibility of self-screening of the kidney function. These results show specific findings, however the number of patients included in the questionnaire was not high enough to generate significant statistics. Only the mean values are determined. Values such as the standard deviation or 95% confidence levels would not have contributed to more validated results. For a better view on the needs of the patient, more patients from different locations and medical practices should be included. In this research only type 2 diabetes patients were included, because they are related to primary care. Type 1 diabetics are treated by nephrologists. This does not mean that the lab-on-a-chip is not of interest to them. The size of the group is smaller (5%) than the type 2 patients (95%), but their chances of developing kidney failure are equal in white and even higher in non-white individuals [59].

4.3 Primary care

The number of general practitioners interviewed (7), does seem to be sufficient. Because after the 7th interview there was not any new information found. The information was reasonably similar, independent of location and form of practice (solo, duo, and group). Because of a unanimous negative answer towards the necessity of implementing the lab-on-a-chip in the medical practice it was concluded that seven interviewees was adequate.

The primary care level was only approached from a qualitative focus point. Further quantitative analysis among a higher number of GP could have contributed to a further degree of accuracy on patients who might be permitted to use the lab-on-a-chip in the home situation.

All the general practitioners interviewed, were located at the east of the Netherlands. To make sure that no location bias occurred, GPs from other places in the Netherlands could have been interviewed. Based on the limited size and differentiation within the healthcare in the Netherlands, the expectation is that medical practices in other locations, do not give other results.

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4.4 Hospital care

4.4.1 Safety Management System

Chronic diseases and kidney function are becoming more important in the current healthcare setting. The relevance of this disease is highlighted by the introduction of the Dutch Safety Management System. Some information on this program will be presented in the following paragraph to support the relevance of this study. A new system has been developed, the so called Safety Management System (SMS), which the hospitals use for continuous risk analysis, to enter improvements and policy capturing, evaluating and adapting. The ultimate goal of the SMS is to control and decrease the (unwanted) damage to the patients. It does so, because it is a system that is focused on managing risks (identifying, analysing and improving) and controlling risks. Such a safety management system is new in healthcare, but very common in other areas of costumer services. The CEO of Shell-Netherlands advised such a SMS in 2004 [60].

The SMS program was started by five partners, the NVZ (Dutch association of Hospitals), NFU (Dutch Federation of University Centre), Orde (Order of Medical Specialists), LEVV (National Expertise Centre for Nursing and Care) and V&VN (Nurses and Caregivers Netherlands) [61].

The SMS safety program supports the Dutch hospitals by offering them knowledge and a structure toward cooperation, to make a 50% reduction on unwanted and avoidable damage possible [20]. The hospitals have to be accredited before the 31th of December 2012 or they need to have a certificated SMS. They also need to achieve the goals on the 10 stated themes. These ten themes are estimated by the patient safety research done by the NIVEL/EMGO. They concluded that on these themes the most profit was achievable on the area of reducing the unwanted avoidable damage to patients in a hospital. [20]

The 10 themes are related to prevention and early recognition of disease. Management of risk is one of the primary concerns [20]. The focus point that is relevant in this study is the prevention of renal failure in combination with intravascular use of iodine-containing substances. The SMS and the 10 themes all are part of the demands of the Dutch Technology Agreement (NTA) 8009. The NTA and thus the 10 themes can be certificated by existing and accredited institutions like the Dutch HKZ, NIAZ, Lloyds and others. [20]

4.4.2 Generalizability

The preference levels and utility results are a reflection of averages, both within as among hospitals. It is important to realize that there are large differences between these hospitals, difference that need to be considered when implementing a new device. The hospitals included in the preliminary market research were all large peripheral hospitals; no small peripheral or academic hospitals were included. The differences between the hospitals occur primarily because of different settings and goals. Generalizability of the results to other hospitals is not possible with the current results. The preliminary market research was only conducted among 42 specialists in 4 hospitals. To deliver a higher accuracy, more hospitals and experts should be included.

4.4.3 Validity

When designing the content and the lay-out of the scenario analysis some assumptions were made. Probably the most important one is the reduction from nine possible scenarios (2 times 3 variables)

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to seven final described scenarios. Two scenarios were not included in the analysis because these were not named in the qualitative research, the interviews. The benefits from reducing the number of scenarios from nine to seven, is that it is less difficult to make choices about the order of numbers and thus following the advice of Smith and Desvousges. This choice did have an effect on the utilities generated by the ranking analysis. No assurance on the true effect on utility can be given without further research. The utilities and SD values of the location outpatient clinic were high because of the missing scenarios. When these two missing scenarios would have been implemented in the preliminary market research the expectation is that the utility would have decreased, with an end value relatively similar to the utility values of the radiology. This would make the laboratory the location with the highest values on utility. In further research a nine scenarios analysis should be performed. The effects on validity and willingness of professionals on participating need to be weight, after which a decision on importance levels between validity and participation rate can be made.

Related to the lay-out of the form, it could be questioned whether the order of the scenarios would influence the choice of the specialists. When comparing the results, this does not seem to be the case. The answers had too much variation in their distribution to be biased by sequence.

The chosen ranking method, RSM could be discussed. RSM is one of a variety of suggestions in literature for accurate determination of attribute weights. In practice it was hard to determine the weights because assessed weights are always subject to response error. RSM was chosen as the methods for weighing, because rank-order weights and approximate weights are the two best methodologies for this type of research [33].

In relation to the obvious answer that there is no desire to place the lab-on-a-chip on the radiology department for planned patients, it is good to realize who gave these answers. Placing the device on their own floor would mean that the radiologists and radiographers would be responsible, might need training and most importantly would have to make time to test all the scheduled patients. These specialists suggest placing the device on the department of application or at the laboratory. When conducting the same research at the oncology department, the outcome will most likely be the opposite (placement of the lab-on-a-chip at the radiology department or laboratory). Given this expected outcome, placing the lab-on-a-chip at the laboratory might be the recurrent outcome for every department. However, this conclusion cannot be drawn before further research is done. An addition to these results is the question whether use of a lab-on-a-chip on the laboratory would be beneficial if current technique allow blood analysis within the hour. An easier solution to enable time efficiency for the patients might be to perform one hour lab analysis for all scheduled patients. Whether this is feasible and desirable should be concluded after further research.

4.4.4 Overall

Most of the information gathered is retrieved via personal contacts. This might be of influence on the reliability of the data. The interviewee might give the answers that would positively influence the research. Chances on this form of bias are low, because of the explorative focus of the study. There are no definite right or wrong answers in this study. Another argument for a low bias by information gathering was the non-existing personal relationship with the colleagues of the contact persons.

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The specialists at the laboratory are in general responsible for the analysis of all sorts of samples. Unregarded whether the device will be replacing the current technology at the laboratory or replacing it outside the laboratory, the knowledge and opinion of these specialists will be very important. It is not stated that they are not willing to accept a new device for blood analysis outside the laboratory, (which as an example is done by radiographers on blood glucose levels at the PET-scan) but this will depend on the properties of the lab-on-a-chip and the current protocols at the hospital.

The answers given by the specialists on the questions about estimations on costs and benefits were very subjective and given with large uncertainties. Not all specialists were benevolent to answer these additional questions. This will be of influence to the results, a lower N is less accurate and valid. To ensure that the given answers reflect the opinion of the professionals in the hospital care, more specialists need to be included in the research.

In relation to the costs, which are implemented in the results trees, it can be said that without the costs for implementation of the lab-on-a-chip, the cost savings are irrelevant. This statement is valid and additional information should be introduced before accurate conclusions can be drawn.

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5 Conclusion

5.1 General

This research was an explorative investigation of possible regions of interest related to implementation of a technology-driven device. To answer the question 'What is the highest application of a novel lab-on-a-chip technology, measuring creatinine in blood for screening, diagnosis or monitoring of kidney function in Dutch healthcare?' three branches were investigated and one turned out to be of real interest.

5.2 Self-testing and primary care

Literature suggested that patients with diabetes Mellitus type 2 were the appropriate population based on the size. However qualitative and quantitative research indicated that the chances of a lab-on-a-chip being successfully implemented in this medical situation are low.

Patients, especially in the age group up until 60 years old, are more willing to accept the lab-on-a-chip as a self-test. They do set some conditions, such as responsibility and feedback. The incidence of patients who prefer a higher screening frequency than current standard is high and the lab-on-a-chip could meet this desire.

The general practitioners are skeptic, both on implementation at the patients' homes and implementation at the medical practice. The only chances on implementation of the device are related to the possibility of replacing the complete lab. This is far from possible, so implementation will not be realized in the near future.

5.3 Hospital care

Implementing the lab-on-a-chip at the hospitals seems to be the option with the best odds. The severity of the disease (contrast nephropathy) and the size of the population (patients who need a contrast scan) are both very high. From research among specialist from the radiology department it can be concluded that there is a need for this device. The patient populations who would benefit the most are the semi-acute and scheduled patients. The best location for implementation of the device depends on the situation. An appropriate location for screening the semi-acute patients on their kidney function is the radiology department or at the laboratory. For scheduled patients, the specialists indicate placement of the lab-on-a-chip at the department of application or at the laboratory to make screening of the kidney function possible.

5.4 Recommendations

Keeping in mind that this is an explorative research, further research will be necessary to find and study other regions of interest. Within the current study further research would be necessary to be more accurate on the possible health and efficiency benefits. The estimated costs of the lab-on-a-chip versus the benefits should indicate whether implementation in the hospitals setting is possible, and whether one or more departments qualify.

During the qualitative research with specialists from the radiology department, questions were asked about the so called 'walk-in' scans. The response was reasonably negative, however it does seem to be one of the emerging changes in the healthcare setting. Further research on this topic might be very useful for future healthcare settings.

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Annex 1: Medimate

Medimate, the 30th spin-off company of the University of Twente, focuses on developing and introducing solutions for healthcare professionals, patients and researchers by using a unique handheld instrument, the Multi Medimate Reader, which could be used for self-monitoring.

The first product that Medimate in 2010 developed is the Medimate Multi Reader and Licitas Disposable Chip that supports the treatment of patients with manic depressive disorder. This device is shown in figure 16. This instrument makes point of care (PoC) treatments possible. The idea is to further improve the lab-on-a-chip technology to make applications that are suitable for other patients such as kidney disease, coronary heart disease and PKU patients [7].

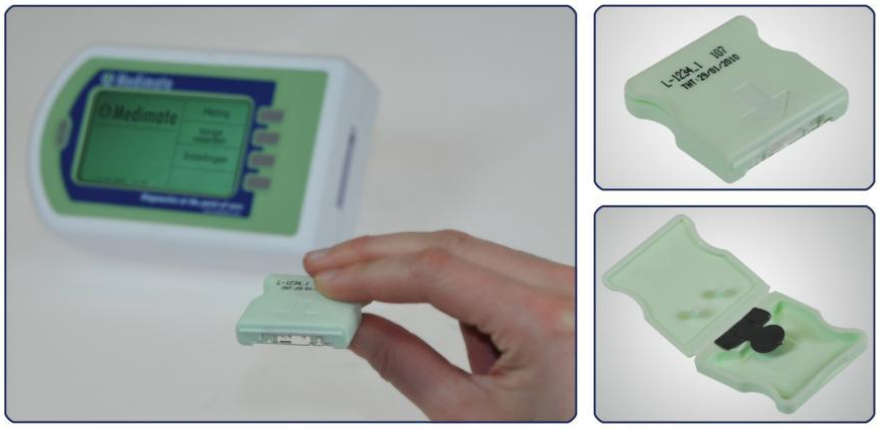

Figure 16 Multireader and disposable chip designed by Medimate

.

Annex 2: Stages kidney disease and MDRD-equation

Stage†	Description	GFR, *mL/min per 1.73 m²*	Prevalence, *n* (%)‡	Action§
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening; chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5 900 000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60–89	5 300 000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7 600 000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400 000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300 000 (0.1)	Kidney replacement (if uremia present)

* CVD = cardiovascular disease; GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.
† Stages 1 to 5 indicate patients with chronic kidney disease; the row without a stage number indicates persons at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m^2 for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
‡ Prevalence for stage 5 is from the U.S. Renal Data System (1998); it includes approximately 230 000 patients treated with dialysis and assumes 70 000 additional patients not receiving dialysis. Prevalence for stages 1 to 4 is from the Third National Health and Nutrition Examination Survey (1988 to 1994). Population of 177 million adults age 20 or more years. Glomerular filtration rate is estimated from serum creatinine measurements by using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated by using untimed urine samples to determine the albumin–creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage. The proportion of persons at increased risk for chronic kidney disease has not been estimated accurately.
§ Includes actions from preceding stages.

Figure 17 Overview five stages of kidney failure [62]

MDRD equation: [62, 63]

*GFR (*mL/min per 1.73 m^2)= 186 *$SCr^{-1.154}$ * $Age^{*0.203}$ (*0.742 if female) (* 1.210 if African-American)

.

Annex 3: Interview – Patients (Dutch)

Diabetes

1. Hoe lang geleden bent u gediagnosticeerd met diabetes

……Jaar

2. Welk type diabetes hebt u?

Type 1

Type 2

3. Gebruikt u medicatie voor uw diabetes, zo ja welke?

Ja/ nee,

……

……

4. Hoe vaak bezoekt u de huisarts in verband met uw diabetes?

……per maand / per jaar (omcirkelen wat van toepassing is)

Screening op verminderde nierfunctie?

5. Bent u gediagnosticeerd met een afnemende nierfunctie?

Ja/nee

6. Hoe vaak per jaar wordt/werd u gescreend op uw nierfunctie?

…….. keer per jaar.

7. Bent/was u tevreden met de frequentie van screening naar uw nierfunctie?

Ja/nee,

Als nee, wat is de voor u gewenste frequentie voor screening per jaar?

…….. keer per jaar.

8. Op welke locatie wordt/werd u voor gescreend naar uw nierfunctie?

Thuis

Ziekenhuis

Huisarts

Elders, namelijk……..

9. Ziet u dit als een geschikte locatie voor de screening?

Ja/nee

Lab-on-a-chip

10. Bent u bekend met de nieuwe technologie lab-on-a-chip?

Ja/nee

Een lab-on-a-chip is een apparaat met daarop een of meerdere minuscule laboratoria. De chip is niet groter dan enkele vierkant millimeters of centimeters. Het grote voordeel van de chip is dat zogenaamde Point of

.

Care mogelijk is. Dit betekend dat het apparaat een zelf toe te dienen monster van bloed of urine nodig heeft, deze direct analyseert en een conclusie trekt over de aanwezige stoffen. Een uitslag over suikerniveaus in het lichaam, maar ook over de functie van de nieren is dan direct (binnen enkele minuten) te geven.

11. Wat is naar uw idee de ideale locatie om een dergelijke test uit te voeren en door wie?
    Thuis – zelf

    Thuis – verpleegkundige

    Huisartsenpraktijk – Arts

    Huisartsenpraktijk – Assistente

    Ziekenhuis

    Anders, namelijk……

12. Denkt u dat u met behulp van een lab-on-a-chip zelf in staat bent om nierfunctie te bepalen?
    Ja/nee

13. Is zelf/thuis screening naar uw mening gewenst?
    Ja/nee

14. Waarom wel/niet
    ……
    ……
    ……

15. Welke voorwaarden stelt u voordat u screening thuis zou uitvoeren?
    ……
    ……
    ……
    ……
    ……
    ……

16. Met deze nieuwe technologie verandert dan uw voorkeur voor de screenings frequentie
    Ja/nee, namelijk…… keer per jaar

17. Kunt u omschrijven wat volgens u het ideale scenario is betreffende screening naar een afnemende nierfunctie?

……
……
……
……
……

.

Annex 4: Interview – General practitioner (Dutch)

Introduction (diabetic care and kidney disease)

1. Wie zijn er binnen deze praktijk betrokken bij de behandeling van patiënten met diabetes en wat zijn hun taken? CP

……
……
……
……
……

2. Wat is de huidige screenings frequentie op nierfalen bij diabeten in deze praktijk? CP

…… keer per jaar

3. Welke methode / technieken gebruikt om een nierfunctie bepaling bij patiënten te doen? CP

……
……
……

4. Is de huidige technologie/methode goed genoeg volgens de hedendaagse maatstaven betreffende behandeling van chronisch zieken? CP

Ja /nee

5. Op welke gebieden binnen de screening naar nierfalen zijn volgens u de meeste verbeterpunten te behalen?

……
……
……

6. Welke acties worden ondernomen als een patiënt gediagnosticeerd is met nierfalen?

……
……
……

Diabetic and kidney disease screening – Ideal situation

7. Wat is in uw opinie de meest gewenste screenings frequentie bij diabeten?

…… Keer per jaar

8. Is dit een continue screeningfrequentie, of spelen andere factoren hier een rol bij?

Continu/ andere factoren namelijk:

……
……

9. Is het in het belang voor de patiënten om nierfalen eerder te detecteren?

Ja/ nee

10. Hoe verandert de behandeling bij deze patiënten bij eerdere diagnose?

……
……
……

.

11. Denkt u dat patiënten bereid zijn/ willen dat er iets verandert in het huidige screeningssysteem?

Ja/nee, want,

……
……
……

12. Denkt u dat een verandering in het huidige screeningssyteem noodzakelijk is i.v.m. de werkdruk bij de specialisten?

Ja / nee want,

……
……
…….

13. Denkt u dat specialisten bereid zijn/ willen dat er iets verandert in het huidige screeningssyteem?

Ja/ nee want,

……
……
……

14. Bent u bekend met het eerdere landelijke methodes om nierfalen tegen te gaan?

Ja / nee

15. Wat is volgens u de reden dat de 'stop nierfalen actie nu' van 2006 niet succesvol geworden is? ECP

……
……
……

Lab-on-a-chip

16. Hebt u wel eens gehoord van zogenaamde ' lab-on-a-chip' technologie?

Ja/nee

Een lab-on-a-chip is een apparaat met daarop een of meerdere minuscule laboratoria. De chip is niet groter dan enkele vierkant millimeters of centimeters. Het grote voordeel van de chip is dat zogenaamde Point of Care mogelijk is. Dit betekend dat het apparaat een zelf toe te dienen monster van bloed of urine nodig heeft, deze direct analyseert en een conclusie trekt over de aanwezige stoffen. Een uitslag over suikerniveaus in het lichaam, maar ook over de functie van de nieren is dan direct (binnen enkele minuten) te geven.

17. Wat is uw mening over het meten van ziektebeelden middels een dergelijk point of care test?

……
……
……

18. Wat zijn naar uw mening de parameters die getest moeten worden door een dergelijk apparaat om sensitief en specifiek te kunnen meten naar nierfunctie?

……
……
……

19. Denkt u dat bij het screenen naar nierfunctie patiënten met diabetes de aangewezen groep is?

Ja / nee

20. Waarom denkt u dit, zo nee welke groep dan?

.

……
……
……

21. Welke eigenschappen moet een dergelijk apparaat naast het betrouwbaar detecteren van het ziektebeeld nog meer hebben om een succes te worden?

……
……
……

22. Ziet u in uw praktijk een toekomst voor het gebruik van een lab-on-a-chip voor het diagnosticeren van nierfalen bij diabeten?

……
……
……

23. Wat zijn de belangrijkste contra-indicaties betreffende implementatie van dit apparaat in uw praktijk?

……
……
……

24. In welke situatie is een dergelijke test nuttiger, thuis, bij de huisarts of elders?

Thuis / Huisarts

Elders namelijk……..

25. Waarom ziet u deze locatie als meest geschikt?

……
……
……

26. Wie uit deze praktijk denkt u dat het meeste te maken zal krijgen met het gebruik van een dergelijk apparaat na implementatie?

……
……
……

27. Denkt u dat de lab-on-a-chip methode zal leiden tot betere kwaliteit van leven voor de patiënten?

Ja / nee

28. Welke verbeterpunten in het leven van de patiënt denkt u te kunnen behalen met de nieuwe technologie?

……
……
……

Afsluiting

29. Hoe zou u het ideale screeningsapparaat voor diabeten die getest moeten worden op nierfalen omschrijven (zonder beperkingen)?

……
……
……

.

Annex 5: Interview– Radiologists and radiographers (Dutch)

Protocol contrast scan

1. Kent dit ziekenhuis een vast protocol voor patiënten die komen voor een contrast scan?

   Ja / nee

2. Kunt u beschrijven wat er in dit protocol staat, wat gebeurd er met een patiënt die voor een contrast scan dit ziekenhuis in komt?

   ……
   ……
   ……
   ……
   ……

3. Wordt voor alle patiënten een kreat en GFR aangevraagd voordat ze een contrast scan ondergaan?

   Ja / nee

4. Zo nee, hoe wordt bepaald voor welke patiënt wel en voor welke patiënt niet?

……
……
……

5. Bij hoeveel procent van de patiënten wordt de nierfunctie van te voren aangevraagd?

……..%

6. Wat is de belangrijkste reden dat op dit moment niet voor alle patiënten gedaan wordt?

……
……
……

7. Belangrijk ongewenst gevolg van onbekende nierfunctie en een contrast scan is een Contrast Induced Nephropathy. Komt dit ziektebeeld ook voor in dit ziekenhuis

   Ja / nee

8. Hoe wordt daar op dit moment mee omgegaan?

……
……
……

9. Wordt het aantal incidenten met CIN gerapporteerd?

   Ja / nee

10. Zijn er nog andere redenen waarom u de nierfunctie voor een contrastscan bij een patiënt zou willen bepalen?

……
……
……

.

Lab-on-a-chip en logistiek

1. Bent u bekend met de zogenaamde lab-on-a-chip technologie?

Ja / nee

Een lab-on-a-chip is een apparaat met daarop een of meerdere minuscule laboratoria. De chip is niet groter dan enkele vierkante millimeters of centimeters. Het grote voordeel van de chip is dat zogenaamde point of care mogelijk is. Dit betekent dat het apparaat een zelf toe te dienen monster nodig heeft, deze direct analyseert en een conclusie trekt over de aanwezige stoffen. Een uitslag over suikerniveaus in het lichaam, maar ook over de functie van de nieren is dan direct (binnen enkele minuten) te geven.

2. Zal een dergelijk apparaat ingezet worden bij acute en of bij geplande diagnostiek?

Acuut / gepland

3. Welke eigenschappen moet het apparaat bezitten om nuttig te zijn t.b.v. nierfunctie bepalingen op deze afdeling? (ICT, gebruiksgemak)

……
……
……

……
……

4. Wat is de meest geschikte locatie om deze test uit te laten voeren en door wie?

……
……
……

5. Welk tijdsbestek zit er nu tussen het bepalen van de nierfunctie en de scan?

…….. dagen/weken

6. Is het wenselijk deze tijd in te korten?

Ja / Nee

7. Zijn er logistieke verbeteringen te maken als de nierfunctie middels deze technologie betrouwbaar op de afdeling radiologie geprikt wordt?

Ja / nee

8. Hoe ziet u dit dan voor zich?

……
……
……

9. Is de afdeling Radiologie de juiste afdeling voor deze test?

Ja / nee

Omdat,……
……
……

10. Het invoeren van deze test op de afdeling Radiologie is een extra taak. Zou deze technologie toch werkdruk verlagend uit kunnen pakken?

.

Ja / nee

……
……
……

11. Denkt u dat patiënten deze techniek en de invloed op het proces als iets positiefs zullen ervaren?

Ja / nee

12. Bent u bekend met het kostenaspect van de huidige nierfunctiebepaling?

Ja / nee

13. Is het van cruciaal belang dat dit apparaat goedkoper dan wel even duur is als de huidige bepaling, of mag het duurder zijn (voordelen en mogelijkheden wegen zwaarder?)

Ja / nee

Omdat,……
……
……

Walk-in principe

1. Wordt er in dit ziekenhuis reeds (deels) gewerkt met inloop scans?

Ja / nee

2. Ziet u voordelen van een lab-on-a-chip als er overgestapt naar meer inloop-scans, zo ja, hoe?

Ja / nee

……
……
……

.

Annex 6: Preliminary market research (Dutch)

Ranking ten behoeve van gebruik van 'Lab-on-a-chip' bij patiënten die een CT contrast scan ondergaan.

Wat is een lab-on-a-chip? Een lab-on-a-chip is een apparaat met daarop een of meerdere minuscule laboratoria. De chip zelf is niet groter dan enkele vierkante millimeters of centimeters. Het beste is dit apparaat te vergelijken met de glucosemeter bij de PET scan. Ook hier wordt een monster (bloed of urine) op de chip geplaatst waarna het in een handzaam apparaat geplaatst en geanalyseerd wordt. Het grote voordeel van de chip is dat zogenaamde point of care mogelijk is. Dit betekent dat het apparaat een zelf toe te dienen monster nodig heeft, deze direct analyseert en een conclusie trekt over de aanwezige stoffen. Een uitslag over suikerniveaus in het lichaam, maar ook over de functie van de nieren is dan direct (binnen enkele minuten) te geven. In dit geval moet uitgegaan worden van een apparaat dat de GFR waarde (volgens de MDRD standaard) weergeeft.

Hieronder staan enkele situaties geschetst. Voor een kwantitatief onderzoek (getallen), wordt u gevraagd om de verschillende scenario's te normeren. Schrijf een 1 bij het scenario waarbij de inzet van de beschreven technologie het meeste nut heeft. Schrijf een 7 bij het minst toepasbare scenario. Let op: alle cijfers (1,2,3,4,5,6,7) mogen maar één keer ingevuld worden!

	U hebt te maken met een 'super acute patiënt' (aorta dissectie), het apparaat is aanwezig op de afdeling Radiologie. De laborant gebruikt het apparaat om de GFR te bepalen voor post-hydratie doeleinden.
	U hebt te maken met een 'super acute patiënt' (aorta dissectie), het apparaat is aanwezig op het Laboratorium. U piept de verantwoordelijke bij het lab op voor een spoedbepaling ten behoeve van de GFR voor post-hydratie doeleinden.
	U hebt te maken met een semi-acute patiënt (longembolie), het apparaat is aanwezig op de afdeling Radiologie. De laborant gebruikt het apparaat om de GFR te bepalen voor de afweging met of zonder contrast en de prehydratie en post-hydratie doeleinden.
	U hebt te maken met een semi-acute patiënt (longembolie), het apparaat is aanwezig op het Laboratorium. U piept de verantwoordelijke bij het lab op voor een spoedbepaling ten behoeve van de GFR voor de afweging met of zonder contrast en de prehydratie en post-hydratie doeleinden.
	U hebt te maken met een geplande patiënt (buik-onderzoek). De patiënt is doorgestuurd vanaf de aanvragende poli en komt nu langs de afdeling Radiologie waar de GFR bepaling wordt uitgevoerd. De laborant of doktersassistente gebruikt het apparaat om de GFR te bepalen en mogelijke pre hydratie te constateren.
	U hebt te maken met een geplande patiënt (buik-onderzoek). De patiënt is doorgestuurd vanaf de aanvragende poli, waar al door de aanvragende poli / arts de GFR bepaling met het apparaat uitgevoerd is. De patiënt komt daarna direct met de uitslag langs de afdeling Radiologie voor een afspraak voor de scan.
	U hebt te maken met een geplande patiënt (buik-onderzoek). De patiënt is doorgestuurd vanaf de aanvragende poli, via het Laboratorium gekomen waar zijn GFR bepaald is met het apparaat. De patiënt komt daarna direct met de uitslag langs de afdeling Radiologie voor een afspraak voor de scan.

Vul aan de hand van het door u gekozen 'meest toepasbare scenario' de volgende punten in:

.

Gekozen scenario:……..

Tijdsbesparing (Hoeveel tijd wordt er voor het ziekenhuis per patiënt bespaard d.m.v. snelle GFR bepaling t.o.v. huidig protocol)

0 Geen besparing
0 Een kleine besparing (<5min)
0 Een grote besparing (>5min)

Tijdsbesparing (Hoeveel tijd wordt er voor de patiënt bespaard d.m.v. snelle GFR bepaling t.o.v. huidig protocol)

0 Geen besparing
0 Een kleine besparing (minuten)
0 Een grote besparing (uren-dagen)

Belasting voor de patiënt. Hoeveel wordt het ongemak voor de patiënt verbeterd t.o.v. huidige methode (schatting)?

0 Geen verbetering
0 Kleine verbetering (minder ziekenhuiscontacten, minder prikbelasting etc.)
0 Grote verbetering (snellere en betere behandeling mogelijk, minder complicaties (CN))

Hoe vaak komt, ondanks de richtlijnen een CN voor in uw ziekenhuis (schatting)?

0 0-1% van de mensen die een contrast CT ondergaat
0 1-3%
0 4-9%
0 meer dan 10%

Hoeveel gevallen van CN kunnen voorkomen worden d.m.v. de Lab-on-a-chip (schatting)?

0 Geen
0 1-10%
0 11-25%
0 meer dan 25%

Wat zou voor u de belangrijkste reden zijn u om een snelle GFR bepaling middels Lab-on-a-chip op te nemen in de richtlijnen voor deze patiëntengroep?

- Vermindering aantal CN
- Vermindering van kosten van preventie van CN richtlijnen voor ziekenhuis
- Vermindering van tijdsinvestering voor radioloog/laborant
- Vermindering van tijdsinvestering voor patiënt
- Verminderd ongemak voor patiënt (prikken etc.)
- Anders……..

.

Annex 7: List of interviewees and participating hospitals

Interviewees:

General practitioner

Hengelo(2)

Enschede (1)

Zevenaar (4)

Patients

Total of 22 patients. Inhabitants of the cities Zevenaar and Enschede

Radiologist

's-Hertogenbosch(1)

Leiderdorp(4)

Radiographer

Leiderdorp(6)

Scenario analysis:

Rijnland Ziekenhuis	Leiderdorp
Slingeland Ziekenhuis	Doetinchem
Sint Jansdal	Harderwijk
Zorggroep Twente	Hengelo

.

Annex 8: Graphs patient level

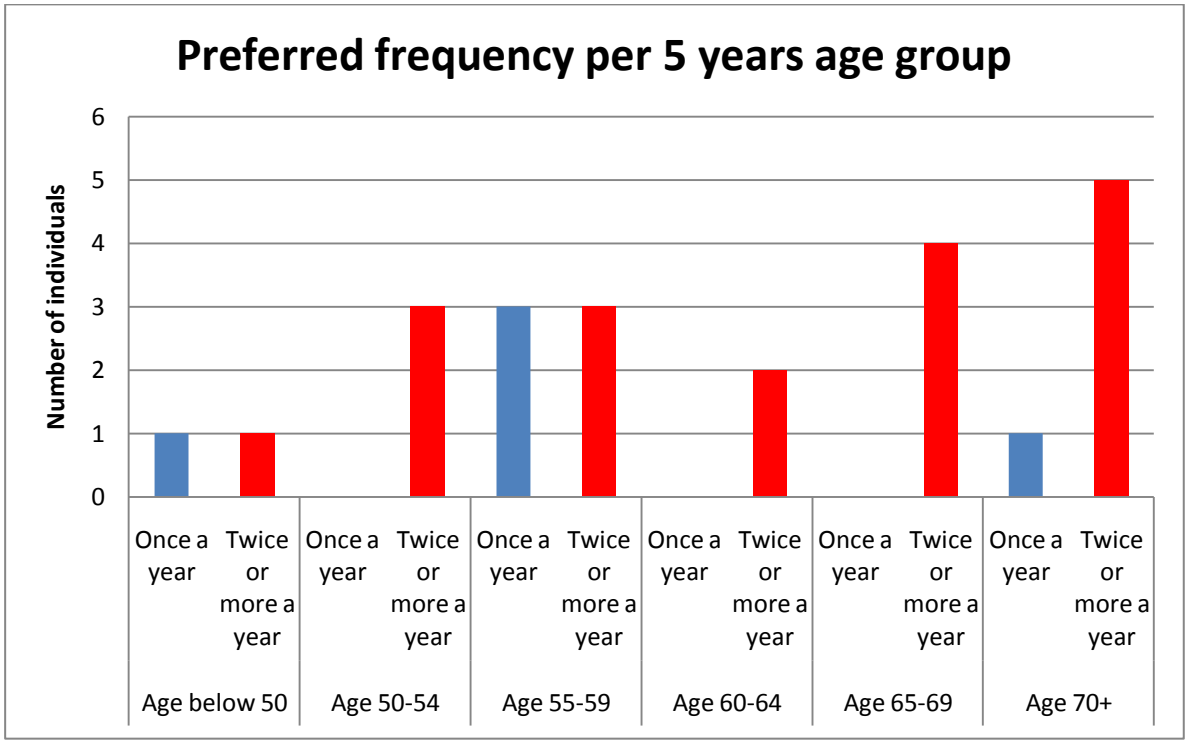

Figure 18 Preferred frequency per 5 years

The desired frequency: Current practice, once a year (blue) versus more than once a year (red). Age groups patients per five years.

- Age group 50-: 50% more than once a year
- Age group 50-54: 100% more than once a year
- Age group 55-59: 50% more than once a year
- Age group 60-64: 100% more than once a year
- Age group 65-69: 100% more than once a year
- Age group 70+: 83% more than once a year

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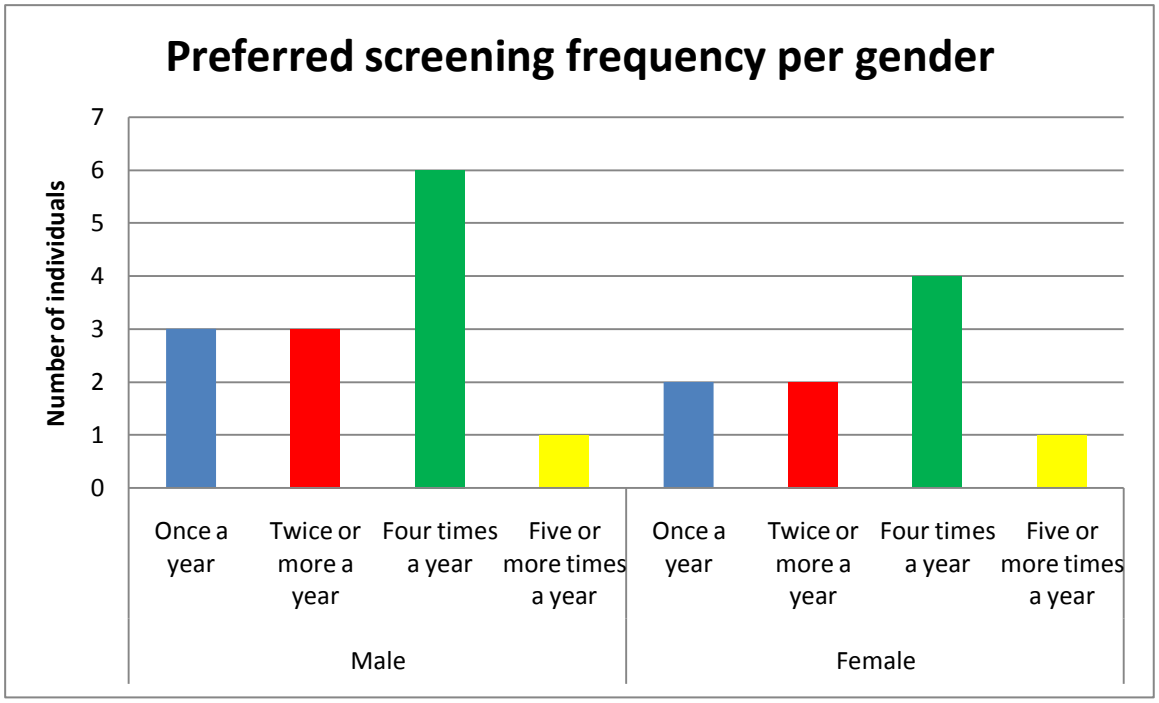

Figure 19 Preferred screening frequency per gender

The desired frequency: Current practice, once a year (blue), versus twice a year (red), four times a year, '3 monthly visit' (green) and more than four times a year (yellow).

Male:

- Once a year: 23%
- Twice a year 23%
- Four times a year: 46%
- Five or more times a year: 8%

Female:

- Once a year: 22%
- Twice a year 22%
- Four times a year: 45%
- Five or more times a year: 11%

.

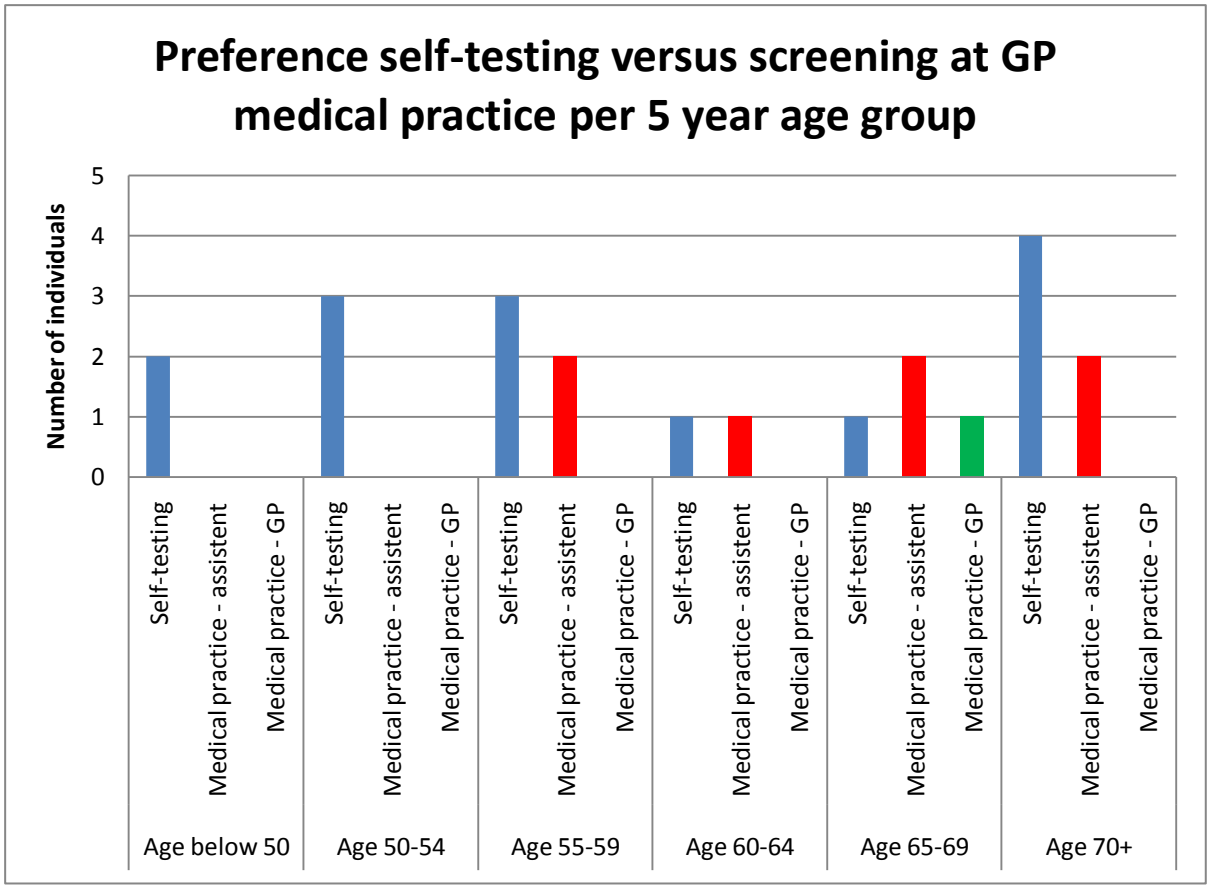

Figure 20 Preference on location per 5 year age group

The desired location: Patients who want to perform the test themselves (blue), patients who want to let it done by the doctors assistant (red) and patients who want the doctor to do it (green). Age groups per five years.

- Age group 50-: 100% self-testing
- Age group 50-54: 100% self-testing
- Age group 55-59: 60% self-testing
- Age group 60-64: 50% self-testing
- Age group 65-69: 25% self-testing
- Age group 70+: 67% self-testing

.

Annex 9: Result-trees

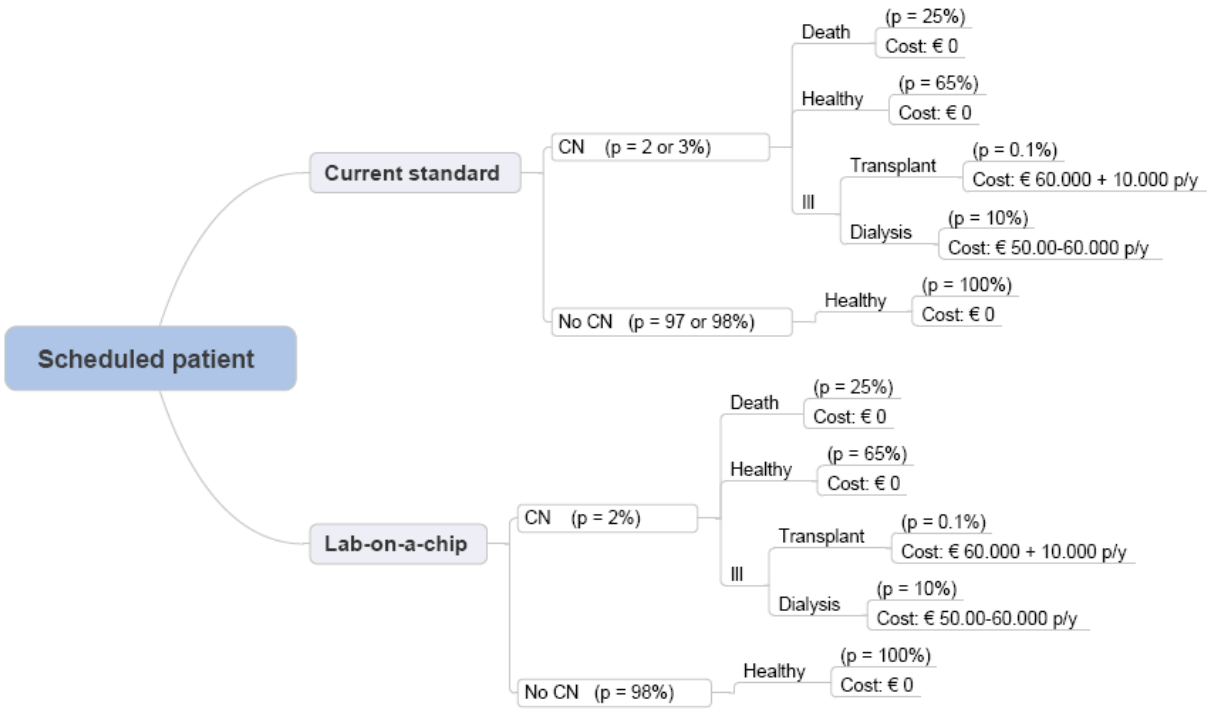

Figure 21 Cost tree - scheduled patients

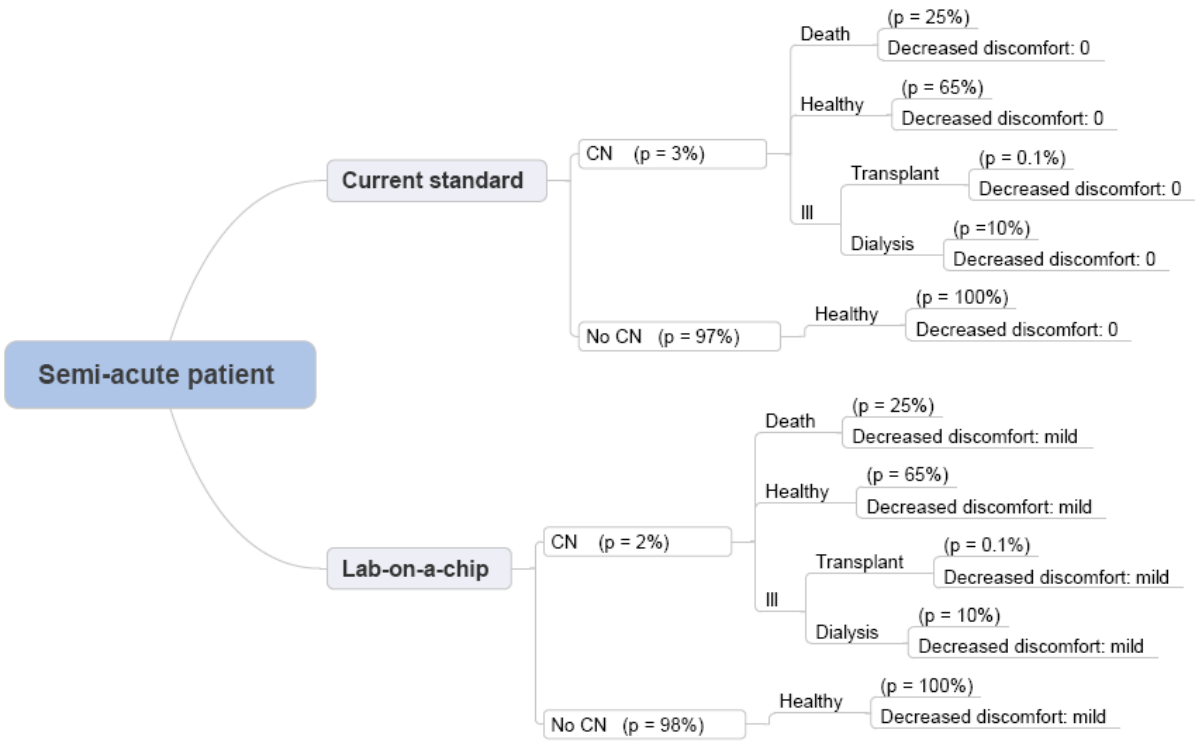

Figure 22 Discomfort tree - semi-acute patients

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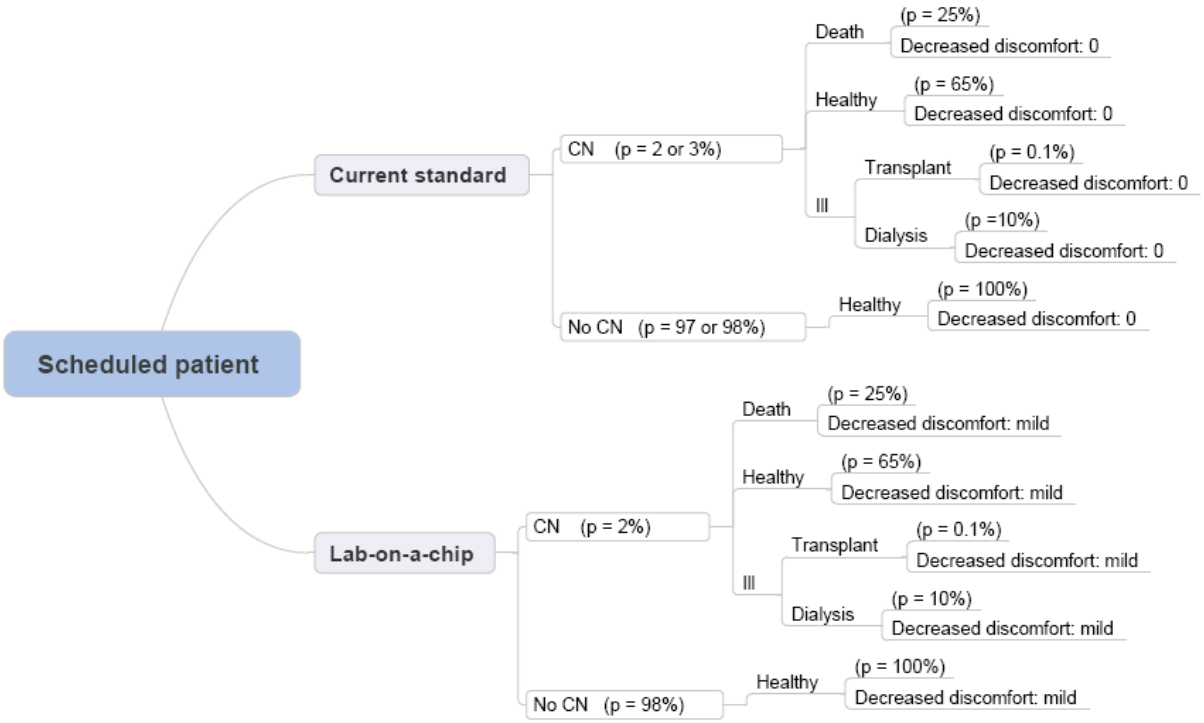

Figure 23 Discomfort tree - scheduled patients

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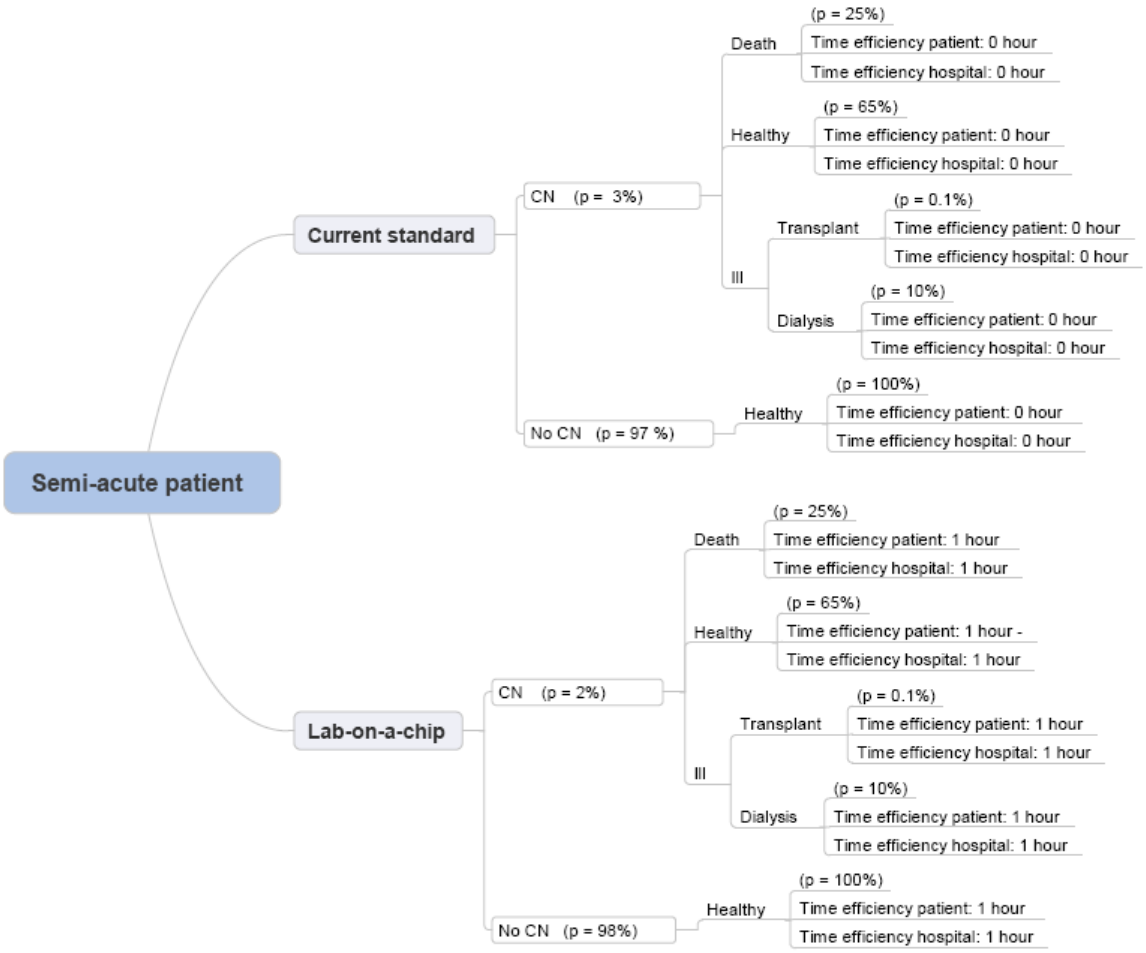

Figure 24 Time efficiency tree - semi-acute patients

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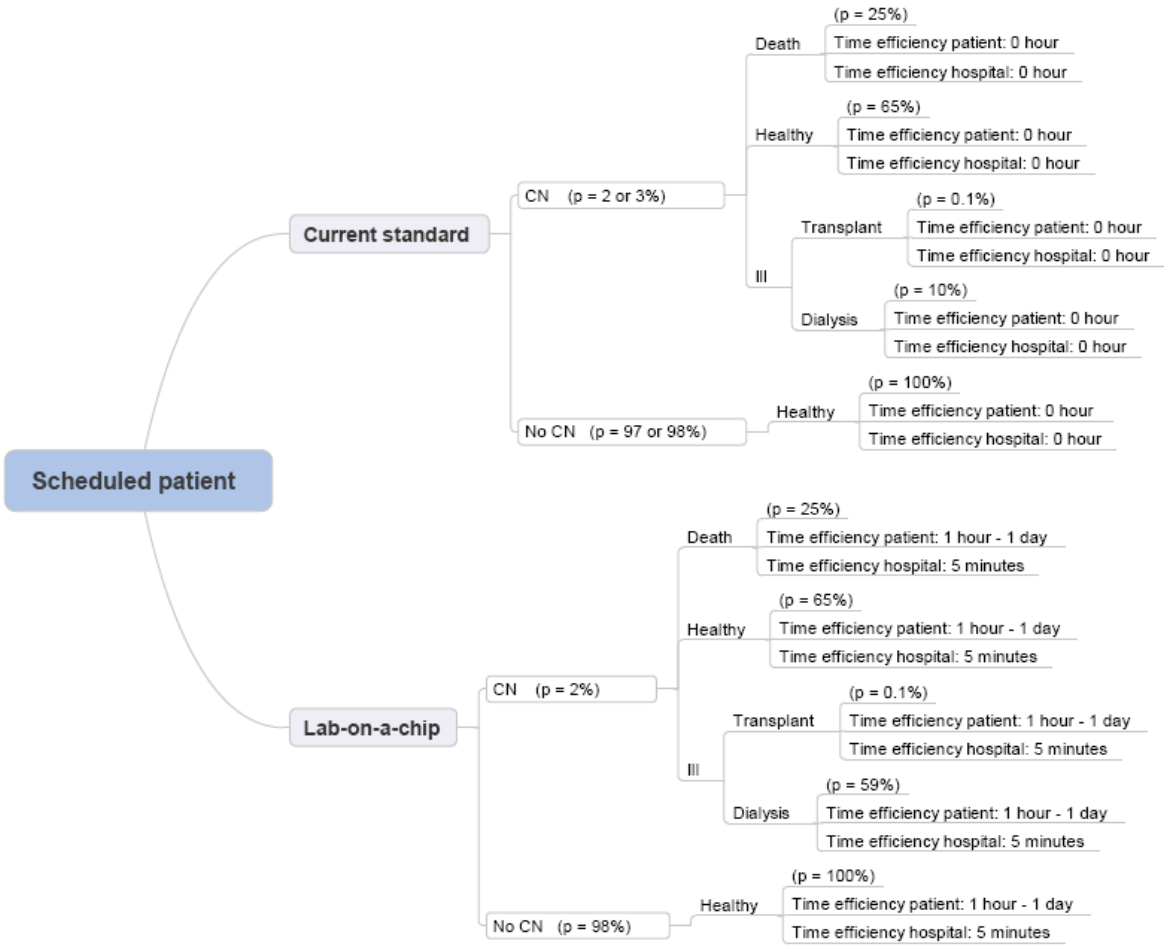

Figure 25 Time efficiency tree - scheduled patients

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Annex 10: Planning of medical product development

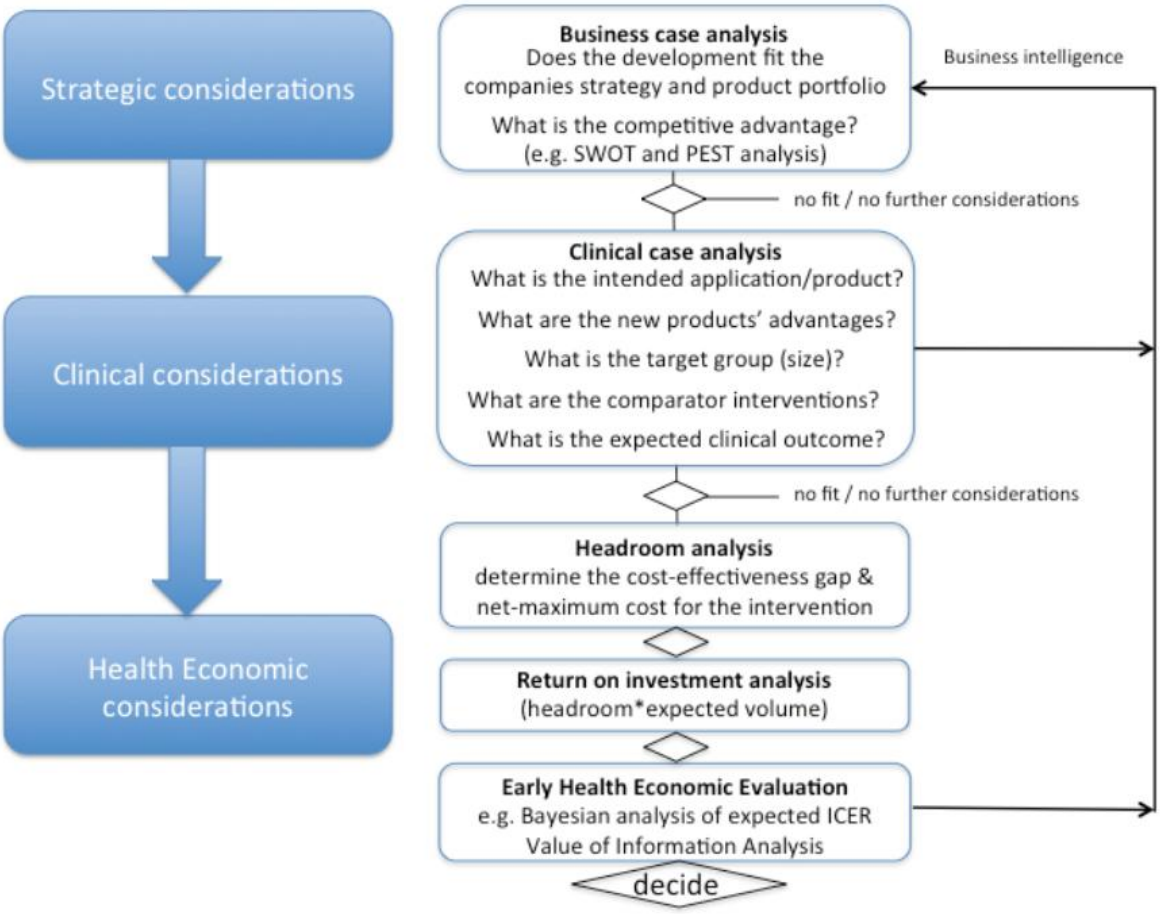

Figure 26 Total graph of 'Planning of medical product development' by IJzerman and Steuten 2011 [14]

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