Universiteit Twente

From PSA testing to screening

A comparison between the Netherlands and the United States of America

Eline Jeckmans
13-5-2008

University of Twente
Enschede - The Netherlands

From PSA testing to screening. A comparison between the Netherlands and the United States of America

Researcher

Eline M. Jeckmans, student Health Sciences at the University of Twente. This research is to achieve her Master of Science (MSc) degree.

Project guidance

Dr. D. Stemerding (University of Twente, STeHPS)

Prof. Dr. W. van Rossum (University of Twente, STeHPS)

Research period

May 2007 – May 2008

Samenvatting

Achtergrond en vraagstelling

In de gezondheidszorg vinden veel veranderingen plaats en het einde van deze veranderingen is nog lang niet in zicht. Elke dag worden er nieuwe technologische innovaties ontwikkeld, die zullen leiden tot veranderingen in de manier waarop de gezondheidszorg georganiseerd is. Een recente trend in the ontwikkeling van medische innovatie zorgt ervoor dat patiënten meer betrokken worden bij hun eigen ziektemanagement; point of care testen (POCT) maken het namelijk mogelijk om laboratorium geneeskunde dichter bij de patiënt te laten plaatsvinden. Hierdoor kan de patiënt zelf meebeslissen en wordt hij of zij daardoor meer betrokken in het proces van diagnostiek en behandeling.

Het doel van dit onderzoek is om de waarde van point of care testen in the Nederlandse gezondheidszorg te bediscussiëren. Vanwege de vele mogelijkheden van point of care testen, zal dit onderzoek zich voornamelijk richten op de prostaat specifieke antigen (PSA) test. Deze PSA test wordt gebruikt om prostaatkanker te monitoren, vast te stellen en op te sporen.

Kanker is doodsoorzaak nummer 1 in Nederlandse mannen, en nummer 2 bij vrouwen. Omdat kanker een belangrijke doodsoorzaak is, en vanwege een toenemend aantal mensen dat gediagnosticeerd wordt met kanker in Nederland, is het veld van de oncologie gekozen als het primaire onderzoeksveld. Het onderwerp prostaatkanker, is gekozen als focus voor dit onderzoek. Dit, omdat de PSA test de mogelijkheid biedt voor vroege opsporing en mogelijke preventie van een van de meest voorkomende types kanker in Nederland.

De centrale vraagstelling van dit onderzoek is daarom als volgt:

> *Wat zijn de ontwikkelingen en verwachtingen in het veld van prostaat specifiek antigen testen en welke gevolgen van deze prostaat specifiek antigen testen op de gezondheidszorg zijn te verwachten?*

Onderzoeksmethode

Er is een vergelijkend onderzoek tussen Nederland (NL) en de Verenigde Staten van Amerika (US) uitgevoerd. Op deze manier kan de centrale vraagstelling beantwoord worden in een breder perspectief. Om deze beide landen te kunnen vergelijken, op een wetenschappelijk verantwoorde manier, is er een theoretisch kader gevormd. In dit onderzoek wordt gebruik gemaakt van een multi level model dat afkomstig is van wetenschaps-

en techniekonderzoek (STS). In dit model wordt de dynamiek van technologieontwikkeling begrepen in termen van co evolutie, wat zoveel betekent als de interactie tussen technologie en maatschappij.

Naast een uitgebreid literatuuronderzoek, zijn er een aantal actoren geïnterviewd die ofwel werkzaam zijn in het veld van prostaatkanker, dan wel in het veld van point of care testen. De actoren zijn geïnterviewd in Nederland and in de staat Californië van Amerika.

Conclusies

Op basis van dit onderzoek kunnen de volgende conclusies getrokken worden:

- De manier waarop de PSA test geïntroduceerd werd in Amerika en in Nederland verschilde vanwege drie factoren; de tijd waarop de PSA test voor het eerst werd geïntroduceerd, de gezondheidszorg waarin het werd geïntroduceerd (de op preventie gerichte gezondheidszorg van Amerika en de meer curatieve Nederlands gezondheidszorg), en de cultuur van het land waar de test geïntroduceerd werd. Nederland is meer terughoudend in het implementeren van innovaties, terwijl Amerika meer agressief is.
- De introductie van de PSA test in Nederland, en breder genomen de point of care testen, hebben invloed op de manier waarop zorg aangeboden wordt en op de manier waarop de gezondheidszorg georganiseerd is. In Nederland is een verandering gaande van een curatieve gezondheidszorg naar een meer op preventie gerichte Nederlandse gezondheidszorg. Naast deze verandering, zal ook de toenemende emancipatie van patiënten in de toekomst verder toenemen met de komst van point of care technologieën.
- In de toekomst worden meer veranderingen in de gezondheidszorg verwacht vanwege de introductie van point of care testen.

Aanbevelingen

Er kunnen een aantal aanbevelingen gedaan worden, die ervoor moeten zorgen dat de introductie van point of care testen in Nederland wordt bevorderd:

- De Nederlandse overheid en cultuur kunnen gezien worden als terughoudend. Innovaties worden, vanwege het 'poldermodel', niet gemakkelijk geïntroduceerd en geaccepteerd in Nederland. De Nederlandse overheid zou daarom moeten investeren in de economie en de markt waarin de innovatie geïntroduceerd wordt, in plaats van terughoudend te zijn in het ondermenen van actie.

- Het 'poldermodel' impliceert ook dat er veel discussies plaatsvinden, voordat beslissingen genomen worden. Om tijd te beslaperen, en om te voorkomen dat het wiel keer op keer opnieuw uitgevonden wordt, zal de Nederlandse overheid moeten kijken naar andere overheden. Op deze manier kunnen onderzoeken en discussies uit andere landen meegenomen worden in beslissingen, zonder dat alles zelf bediscussieerd moet worden.
- De Nederlandse overheid en de Nederlandse gezondheidszorgsector zouden beide de verandering van een curatieve naar een preventieve gezondheidszorg moeten bevorderen. Met het gebruik van point of care testen kan deze verandering ervoor zorgen dat veel tijd, geld en mogelijk ook levens gespaard worden.
- Er is veel onzekerheid ontstaan, omdat er niet veel informatie beschikbaar is over point of care testen. Deze onzekerheid kan leiden tot patiënt en of maatschappelijke angst vorming. De Nederlandse gezondheidszorg, en de bezorgers van point of care testen kunnen zich hiervoor beschermen door betere informatie te verstrekken.

Abstract

Background and prime question

The health care sector is subject to a lot of changes, with the end not yet in sight. Technological innovations are developed every day, which will lead to changes in the way health care is organized. A recent trend in technology development addresses the need of patients becoming more closely involved with their disease management. Point of care tests (POCT) offer the possibility of bringing laboratory medicine closer to the patient, which enables the patient to be more involved.

The aim of this research is to discuss the value of point of care tests in the Dutch health care system. However, due to the broad possibilities of point of care tests, this research will focus on one specific point of care test; that is the prostate specific antigen (PSA) test. The PSA test is used to monitor, diagnose and detect prostate cancer in men.

In the Netherlands, cancer is the primary cause of death among men and the second amongst women. Due to cancer being the most important cause of death and due to the increased incidence, the focus of this research is the development of POCT in the field of oncology. In the light of this social interest, the focus chosen for this research reflects on the possibility of early detection and possible prevention in one of the most common type of cancer amongst men, next to lung cancer; that of prostate cancer.

The prime research question of this research, therefore is:

> *What are the developments and expectations in the field of prostate specific antigen tests and what impacts of this prostate specific antigen test are likely to be expected on health care?*

Research methodology

A comparative study between the Netherlands (NL) and the United States of America (US) is executed so that the prime question can be answered in a broader perspective. In order to compare both countries in a scientific manner, a theoretical starting point was chosen. In this research a multi level model is used that is derived from the science and technology studies (STS). In this model the dynamics of technology development is understood in terms of co evolution, which means the interaction of technology and society.

Next to an extensive literature research, different actors in the field of prostate cancer as well as in the field of point of care technologies, were interviewed in the Netherlands and in the State of California of the United States of America.

Conclusions

On the basis of this research, the following can be concluded:

- The way the PSA test was introduced in the United States of America and in the Netherlands differed due to three main factors; the time in which it was first introduced, the health care sector in which it was introduced (preventive orientated in the United States of America, and cure and care orientated in the Netherlands), and the culture of the country in which the PSA test was introduced. The Netherlands is more withholding in adopting innovations, while the United States of America is more aggressive.
- The introduction of the PSA test in the Netherlands, and POCT in a broader term, influences the way health care is provided and organized. There is a shift noticeable from cure and care towards more preventive health care. Also the emancipation of patient will grow further with the introduction of point of care technologies.
- In the future more changes in health and the health care sector can be expected due to the introduction of point of care tests.

Recommendations

Some recommendations are made in order to improve the introduction of point of care tests in the Netherlands. Because these recommendations can influence each other, they are stated at random:

- The Dutch government and culture can be considered as somewhat withholding. Due to this 'poldermodel', innovations are not introduced and adopted easily. The Dutch government should however stimulate both the economy and the market in which the innovation is introduced, instead of being withholding in taking action.
- The 'poldermodel' also implies a lot of discussions are held prior to decision making. In order to safe time, and to prohibit that the wheel is re-invented time after time, the Dutch government should benchmark. This way, research performed and discussions held in other countries, can be taken into account without doing it all over again.
- The Dutch government and the health care sector both should encourage the shift from cure and care towards a more preventive orientated health care sector. Using point of care tests, this shift can save a lot of time, money and possibly lives.
- Because not much information is available on this new subject of point of care tests, this uncertainty could lead to (patient or society) anxiety. The health care sector, and providers of these tests, can anticipate on this by offering more unambiguous information.

Table of Contents

Acknowledgements

The health care sector is subject to a lot of changes, with the end not yet in sight. Technological innovations are developed every day, which will lead to changes in the way health care is organized. In the field of point of care technologies these changes are yet to happen. Therefore this is the subject of my Master Thesis, and with that the conclusion of my Master Health Sciences study at the University of Twente in Enschede.

Looking back at the process of graduating and the completion of writing this report, there is still one thing I would like to do: Thank all who made a contribution to this process.

A special thanks to my guest family and roommates in San Francisco, thank you for showing me around and making my stay memorable! I would also like to express my appreciation to all of the people who generously made themselves available for interviews for this research. Although not all have been cited in the course of this text, without their help I could not have completed this research!

I would also like to thank Dr. Stemerding and Prof. Dr. Van Rossum at the University of Twente for their contribution, their critical remarks, their helpful direction, but above all the inspiring conversations that have led to this research. And finally, some words of thanks to my family and friends; thank you for your interest and occasional distraction during my graduation period!

Enjoy reading this thesis!

Eline Jeckmans

1. Theme and central question of the research

1.1 Introduction

Clinical diagnostics is the assessment of the risk of having a certain disease, on the grounds of combinations of test results for patients with the suspicion of having that illness. The major goal of diagnostics is to distinguish between persons who are ill from persons who are not. The diagnostic process normally starts when a person with health complaints consults a doctor. This doctor will then perform one or several diagnostic tests to come up with the right diagnosis. According to D. Sackett et al. (1996), founder of evidence based medicine, a diagnostic test has to have a value for the patient. This means a test should contribute to an accurate diagnosis. It should also help the practice of a specific treatment and it should benefit the patient. This last characteristic of diagnostic testing is becoming more and more significant in current practices of diagnosis and treatment of patients. Social researcher E. Tonkens (2003) wrote a book on people, and patients, becoming more self conscience and more emancipated. According to Tonkens, and several other social researchers (Price, St. John, & Hicks, 2004; RVZ, 2008), patients want to be more involved with their own disease management.

A recent trend in technology development addresses this need of patients becoming more closely involved with their disease management. Point of care tests (POCT) offer the possibility of bringing laboratory medicine closer to the patient, which enables the patient to be more involved (Price, St. John, & Hicks, 2004). This seems rather promising, but what is POCT and why should we embrace this new technology? In this research we shall provide an answer to these questions, by examining the developments and future expectations in the field of POCT. We will also outline the possible impact of POCT in health care, which is characterized by, for example, early detection, prevention, and the growing independent role of health care consumers. The aim of this research is to discuss the value of POCT in the Dutch health care system.

1.2 Focus of the study

As stated in the introduction, POCT offers the opportunity of performing laboratory medicine closer to the patient. These tests can be performed at different health care sites, such as at home, at a work place, at health care centers, in ambulances, in emergency rooms, et cetera (Price, St. John, & Hicks, 2004). As well as different areas in which POCT can be used, at this moment in time there are also a variety of diseases that can be tested using POCT, for example, low or high blood glucose, high cholesterol and the presence of pregnancy (Price & St. John, 2006). Because of the broad possibilities of these tests, this research will focus on one specific point of

care test. Focusing on a specific subject enables us to also learn about the broader context of point of care tests.

Point of care tests is a very broad term; the definition of Price and St. John (2006) is therefore used to clarify the meaning of this term. A point of care test is "*any test that is performed at the time at which the test result enables a decision to be made and an action taken that leads to an improved health outcome*".

1.2.1 Choice of the focus of the research

Improved medical care is one of many factors which results in extending the life expectancy of the population. Although prolonging life is one of the main goals of this improvement, it also increases the incidence of diseases that are strongly correlated with age, such as cancer. In the Netherlands, cancer is the primary cause of death among men and the second amongst women (CBS, 2006). Due to cancer being the most important cause of death and due to the increased incidence, the focus of this research is the development of POCT in the field of cancer. Cancer has been a major topic of interest for Dutch newspapers over the last year, because of the opportunity of early detection and possible prevention of different types of cancer. In the light of this social interest, the focus chosen for this research reflects on the possibility of early detection and possible prevention in one of the most common type of cancer amongst men, next to lung cancer; that of prostate cancer (CBS, 2006).

1.2.2 Prostate specific antigen (PSA) test

Prostate cancer is currently diagnosed using a point of care test called the prostate specific antigen (PSA) test. At this moment in time the PSA test is subject to major (public) debates concerning technological, medical and social consequences. Due to these recent debates the subject of PSA tests has a social and scientific relevance. In this research the prime question is specifically tailored to PSA tests to narrow the research subject. The prime question of this research is;

> *What are the developments and expectations in the field of prostate specific antigen tests and what impacts of this prostate specific antigen test are likely to be expected on health care?*

1.3 Comparison between the United States of America and the Netherlands

A comparative study between the Netherlands (NL) and the United States of America (US) is executed so that the prime question can be answered in a broader perspective. In the US a lot of research is performed in the field of technological development, and due to the American culture a lot of these innovations are

implemented and accepted quite easily (Achterhuis, 1997). This will also be the case for point of care technologies. The United States of America can therefore be seen as a model which allows us to detect trends, that may, or may not, occur in the Netherlands when implementing POCT. Because practices in the United States of America differ from state to state, we will focus on one state. The state of California is chosen because of the high concentration of technology (developing) organizations, in the Silicon Valley.

1.3.1 Prostate specific antigen (PSA) test

The most recent introduction of POCT in the field of prostate cancer in the Netherlands is the PSA self test. This test has been introduced in the US approximately five years ago. Exploring the developments of the introduction of this PSA self test in the United States of America and its implications allows us to translate it to the Dutch practice. This way the Netherlands can prepare for different possible scenario's in the field of PSA tests.

1.3.2 Outline of the report

A comparison study requires a clear outline of both the way the research is set up and the way the thesis is outlined. In this research we will distinguish between the American practice and the Dutch practice. First the situation in the US is described, subsequently the situation in the Netherlands. This way the Dutch practice can be compared with the American practice at once.

Chapter one gives a introduction to the subject. Also the theoretical basis is outlined. The second chapter contains the explanation of the theoretical model used. In chapter three more information is given on the subject of prostate cancer. The fourth chapter describes the development and introduction of PSA testing and screening in the United States of America. Chapter five describes the same development and introduction in the Dutch health care sector. Chapter six is about the introduction of point of care technologies in the field of prostate cancer both in the United States of America as in the Netherlands. The conclusion and discussion of this research is given in the last and seventh chapter of this report.

1.4 Theoretical starting point

To gain insight on possible developments, we must take into account the way in which PSA tests were developed over the last years as well as the way they were introduced in the practice, put into a broader context of other relevant developments in the health care sector. That is why in this research a multi level model is used that is derived from the science and technology studies (STS). In this model the dynamics of

technology development is understood in terms of co evolution, which means the interaction of technology and society. Using this model important similarities and differences between the US and the Netherlands are also taken into account.

The multi level model will be outlined and applied to point of care testing in the second chapter of this thesis.

2. A multi level perspective on technology development in health care

The aim of this research is to discuss the value of PSA tests in the Dutch health care sector. An innovation, such as point of care tests, can be evaluated on two aspects, namely the technological value and the social value. The technological value of a medical innovation can be divided into the scientific value and the medical value. If an innovation is of scientific value it contributes to research and development, not only in the medical field, but also in different scientific fields. If an innovation is medically valuable, it can improve health and the health care sector. Next to the technological value, which is clearly important, also the social value of an innovation must be taken into account. According to different scientists, the development of innovations occur in co evolution with society (F.W.Geels, 2002; Geels & Schot, 2007; Rip & Kemp, 1998). But, how can we evaluate the value of POCT and its possible impact on the Dutch health care? A multi level model with respect to the co evolution of technology and society is called for. In this chapter the model used is outlined and applied to developments concerning point of care tests in health care.

2.1 Multi level perspective: Health care and the role of technology development

Figure 2.1 shows the model in an overview. The first level, the micro level, consists of laboratories and clinics as *socio-technical niches*, in which new technological options are explored. The development of new technologies at niche level allow new (and existing) knowledge to be developed further and to get tested in a relative safe environment. Innovations in health care have led to major changes and improvements in the past. One of the most

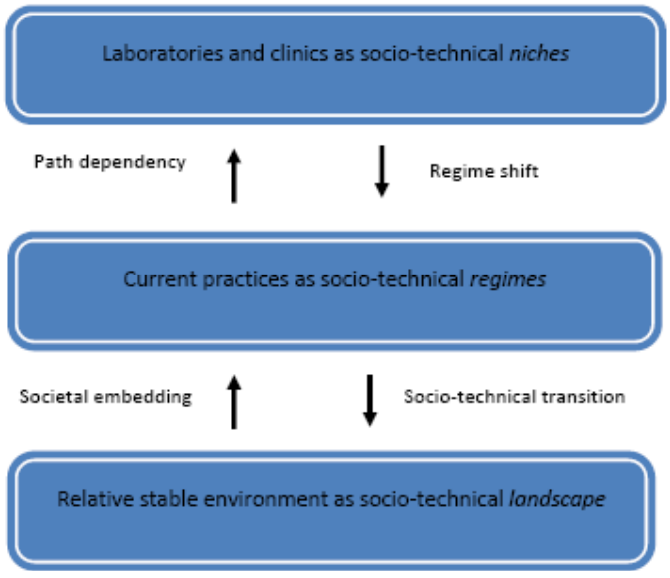


Figure 2.1 Multi level model (Moors, Rip, & Wiskerke, 2004; Rip & Kemp, 1998; Stemerding & Swierstra, 2006)

well known technological innovations is the discovery of the X ray by scientist Wilhelm Conrad Röntgen (1985 1923). In the comfort of his own home he discovered the value of an innovation we nowadays use on a daily basis. For this technology to become so popular the findings of Röntgen needed to be examined further in laboratorial settings, thus at niche level.

The second level, the meso level, is build up of current practices as *socio-technical regimes* which creates opportunities and/or constraints to innovations. A relevant subject in lights of this research, are the so called *diagnostic regimes*. In the health care sector different regimes concerning diagnostics can be differentiated, which all have its own rules and guidelines. For example, there is a *regime of physical examination*. A physician has guidelines for the way a physical examination should be conducted. Other *diagnostic regimes* in health care are the *regime of laboratory diagnostics*, where diagnosis mostly concern fluids such as blood or urine, and the *regime of image based diagnostics*, in which different technologies are used to form an image of the body in order to diagnose the patient.

Over time these and other regimes have been altered, either due to technological changes at niche level, or due to changes at the third level, the macro level, which is a relative stable environment of institutions, infrastructure and established values and beliefs. It can be characterized as a *socio-technical landscape* which enables and/or constrains technological change and the evolution of regimes (Stemerding & Swierstra, 2006). Different landscapes can be distinguished, as there are many different regimes. For the *diagnostic regimes* for example, there is a *diagnostic landscape*. In this landscape values, beliefs, rules and guidelines concerning all different ways of diagnosing are encapsulated. Next to the *diagnostic landscape* there are other landscapes, such as the *landscape concerning public health and screening*.

All levels of this multi level model co evolve with each other. According to Achterberg et al. (2007) the introduction of innovations in society can be seen as a process in which both technology and society are shaped. The introduction of new technologies brings along new expectations, new practices, new skills, and new values, which can lead to changes in e.g. the governmental field. The way this process is formed can be done in different ways:

[1] Path dependency can be described as a development in which established socio technical regimes create opportunities for new technologies and barriers for some others. Let us take the invention of Röntgen, the X-ray, as an example. When the X ray was first introduced to the market, it was a very large machine that could not be moved around easily. The existing diagnostic regime did not see the benefits of this new method, and thought the technology was too large and unpractical. This is an example of a regime that creates barriers for some innovations. In the same diagnostic regime another technology, the thermometer, was also introduced as a medical innovation. Due to the small size of the thermometer and the way the existing regime was organized,

this technology was adopted almost immediately. This process is an example of the same regime creating opportunities for another technology.

[2] Regime shifts require structural changes in society in which the introduction of a new technology may cause a new practice of skills, suppliers, users, rules and values. In the case of the X ray, the technology was not adopted in the existing diagnostic regime. Health care was not used to see the inside of a body, without opening the body by performing an operation. Due to changing opinions and values the importance of the X ray became clearer. However, the technology was very different from the diagnostic tools used prior to the discovery, so that a new regime of image building diagnostic was formed. Which, in turn, created new opportunities for other image building diagnostics as we now know?

[3] Societal embedding is the embedding of a regime in the existing landscape. When a new regime is formed, as is the case in regime shifts, this regime can embed in the existing landscape. This means that all necessary legal, economic and socio-cultural beliefs of the existing society and landscape do not have to be altered for the new regime to survive. In case of the X ray the new regime that was formed could not embed easily in the existing landscape, because e.g. new laws needed to be drawn up.

[4] Socio-technical transition is formed by technological changes and regime shifts. It consists of instabilities which are formed by e.g. economic, socio cultural and institutional changes. In this last case a regime shift can lead to new structural relationships between individual health care, health promotion and public health policies. This was the case with the X ray, because of technological difficulties, the technology itself had to be altered. The machine was made smaller and more portable, in order to meet the criteria's of the existing regime. When the X-ray was introduced ones again, a new regime was made (regime shift). Due to this new regime, the existing landscape was not sufficient enough and also needed to be altered.

2.3 Development of point of care tests

Using the multi level perspective, the development of the broader context of point of care tests can be evaluated. First an overview of the different technologies is given, which can be considered as the niche level of the model. Second the practice of diagnosing diseases in health care sectors in the western world is described at regime level. Further more important factors at landscape level are discussed, such as economic, political and cultural factors concerning point of care tests in health care. This description of the model is specialized for the theme of this research, namely the development of point of care tests as a contribution to early detection and preventive care. At the last part of this paragraph the extent to which the development of point of care tests fits in the existing landscape of health care and the extent to which this requires change in which technology and/or landscape needs to be fitted also is discussed.

2.3.1 Niche level

Point of care test can be discussed from different point of views. It can be categorized by looking at the technological characteristics, at the different practices in which point of care tests can be used and by looking at the different actors whom can use the tests. According to Price, St. John and Hicks (2004; 2006), there are three different forms of POCT:

[1] Handheld devices are diagnostic tests that can be carried quite easily as they are of a small size, and contain all necessary parts for performing and reading the test. The most common type of handheld devices, is the dipstick. A sample, mostly urine or blood, is applied in a porous substance, which will react with a dry substance. This dry substance reacts with the sample, if the test is positive. The most well known example of this type is the pregnancy test. The development of this easy form of handheld devices is still going on. Different ways of reading the outcome of these tests are developed. If we take the pregnancy test as an example, first the test was read with one or two stripes, than the possibility of a plus (+) if pregnant or a minus (**-**) if not pregnant, and the actual word PREGNANT became available as well. With other dipstick tests even different levels can be measure. The extent to which the sample reacts with the substance is measured and described in e.g. numbers or different shades of colors (Price, St. John, & Hicks, 2004; Price & St. John, 2006).

[2] The addition of meter reading with handheld devices offers two major benefits to the interpretation of the measurement. First it enables the person performing the test to interpret the outcome more closely, as it enables quantitation of the signal produced. Using a meter it is possible to read the change in color of the different shades produced by the test, or the change in electrochemical signal. Secondly, a meter decreases the risk of bias due to user variability. A meter reads the test the same way every time it is performed, it can also produce quantitative outcomes instead of qualitative, which are also subject to user variability. The most common known handheld device with meter reading is the blood glucose device. This device is used by diabetics to monitor the level of glucose in their blood, in order to determine whether or not medication is needed (Price, St. John, & Hicks, 2004; Price & St. John, 2006).

[3] Bench top devices are point of care tests that are larger, and can sometimes handle more than one sample at a time. These devices mostly have screens, such as LCD or touch screens, keypads and printers. Bench top devices often are complex machines. The blood gas instruments are the most common forms of bench top devices. It can measure e.g. pH, flow of the blood, glucose level and the quality of the blood all at one time. Using the screen, the test result can be attained almost immediately (Price, St. John, & Hicks, 2004; Price & St. John, 2006).

Due to the technological characteristics and the potential size of point of care tests, these test can be used at different practices and by different actors. Point of care tests are performed in settings, such as at home, at a workplace, at leisure facilities, at pharmacies, at health centers, at diagnostic/treatment centers, inside an ambulance or helicopter, in an emergency room, in operating rooms, inside an intensive care unit or on a ward. All these different practices count for different users of the technology, e.g. there normally is no physician present at home or at work. Next to physicians, other care givers are trained to use POCT. But point of care tests can also be used by patients, such as the blood glucose meter; or by consumers, as is the case with pregnancy tests.

2.3.2 Regime level

The introduction of a new technology in an existing regime can develop in different ways, as described previously in the first paragraph of this chapter. When reading this part of the paragraph, one must take into account that the introduction of point of care tests in different health care sectors has not fully developed yet. Therefore only a glance of the introduction of point of care tests can be captured here.

The first known diagnostic regime was the practice of performing diagnostic tests at the bedside of the patient. In the early beginning of health care, care givers would examine the body and its fluids by smelling, tasting en looking at it. Later on other ways to examine body fluids at the bedside of the patient were developed (Lindeboom, 1993). Technological innovations made it possible to examine the body more closely, while it also made diagnosing an illness a lot more difficult.

New diagnostic tests became more complex, the workload for performing those tests increased and instruments used to perform the tests became more sophisticated, and a new diagnostic regime was born. All this knowledge with regard to diagnosing diseases became centralized in laboratories (Price, St. John, & Hicks, 2004). The diagnostic regime of laboratory medicine changed the way diagnostic tests were performed, as they were now ordered by a physician and performed at a laboratory.

The introduction of point of care tests offer the possibility of diagnostic tests being performed at the clinic once again, only better. This means a new diagnostic regime of point of care diagnosing is waiting around the corner.

Next to the regime shift concerning diagnostics, the regime concerning the focus of health care is starting to change. Due to the increasing double aging, both the population and the people caring for this population are growing older, the focus of the existing health care sector lies mainly on cure and care. Which means most

attention, medically, technologically and financially is given to diagnosing illnesses, developing treatment for illnesses and caring for patients. However, recent events show a shift from cure and care to a more preventive centered health care.

A growing interest of insurance agencies and an increasing interest in populations own health are contributing to this shift. Health care expenditures in the western society are reaching a peak level, and are therefore trying to reduce costs. (Lapré, Rutten, & Schut, 2001) On the other hand, the population is getting more interested and concerned about its health, and is consequently using more and more health care services every day (Tonkens, 2003). This shift can be seen as a regime shift from the cure/care health care regime to a preventive health care regime.

2.3.3 Landscape level

The landscape in which the existing diagnostic regime of health care is embedded consists of an environment of economic, political and cultural factors, and values and beliefs concerning laboratory medicine. When a new regime is formed, in this case the regime of diagnosing at the point of care, the landscape might have to be altered. The existing landscape focuses on health care provided by educated and professional care givers. The introduction of point of care tests enable patients to perform their own tests, thus uneducated persons get control over diagnostic tests. New rules and guidelines on how to handle this responsibility and this accompanying liability are needed.

Economic factors, such as the increasing costs of health care, can create opportunities for new regimes, such as a more preventive orientated health care. Preventive health care can reduce costs by detecting diseases at an early, more treatable stage, which reduces the costs for long treatments and follow up care. Hence, for the new preventive orientated regime, the existing landscape does not have to change radically.

2.3.4 Conclusion

The beginning of diagnostic tests started at the bedside of the patient. In the early beginning of health care, care givers would examine the body and its fluids by smelling, tasting en looking at it. Technological innovations made it possible to examine the body more closely, while it also made diagnosing an illness a lot more difficult. Knowledge with regard to diagnosing diseases became centralized in different laboratories. Diagnostic tests as we are now used to, are ordered by a physician and performed at a laboratory. Point of care tests offer the possibility of diagnostic tests being performed at the clinic once again, only better.

The developments of point of care tests requires the existing landscape to change in order to embed the new diagnostic regime of point of care diagnostics. In the case of point of care tests *regime shifts, societal embedding* and *socio-technical transition* are the case.

2.4 Why focus on PSA tests?

In this research an overview of the development and introduction of PSA tests are discussed. In this research the case study of prostate specific antigen (PSA) test, which is used to diagnose prostate cancer, is chosen after talking to different experts in the field of point of care tests in the Netherlands. Without going into details about the function and possibilities of the PSA test, since this will described in the following chapters, the choice for this point of care test will be made clear in this paragraph.

The PSA test is a diagnostic test that is ordered by a general practitioner or another physician. The patient gives a sample of blood at a laboratory, where the test is performed. The results of this test are then sent to the physician, who will hand over the results to his or her patient. Due to technological developments this PSA test is altered so that everybody is able to perform the test. This means the PSA test has caused a shift from laboratory testing to point of care testing. Due to this change, regimes need to be altered and new regimes are created, which, in return, alters socio-technical landscapes.

According to Price, St. John and Hicks few cancers have generated greater controversy than prostate cancer. So many different policy recommendations have emerged possibly due to technological challenges and the influence of public opinions (2004). Also because of this great public interest and the influence public opinions have on the development and introduction of the PSA test, this also is a case that reflects the aim of this research best.

Because the PSA test has under undergone most of the changes possible according to the multi level model used in this research, this test is particularly suitable for discussing all aspects of the development and introduction of point of care tests in the Netherlands.

2.5 Research questions

The prime question of this study is *What are the developments and expectations in the field of prostate specific antigen tests and what impacts of this prostate specific antigen test are likely to be expected on health care?*

This prime question can be divided into different research questions to answer the prime question. In this paragraph these research questions are made even more explicit using the multi level perspective. Answers to these research questions are given in chapter's four to six of this report.

Micro-level: technological niche

- How can the developments concerning PSA tests be described?
- What expectations do the actors have of PSA tests?
- What expectations does the environment have in which PSA tests are/will be used?

Meso-level: socio-technical regime

- In what way are the existing regimes concerning PSA test organized?
- To what extent and in what way need these regimes be altered?

Macro-level: socio-technical landscape

- In what way are PSA tests and accompanying regimes embedded in organizations, financing, rules and laws at the landscape level of the health care system?

2.6 Methodology

The type of study conducted for this research is a comparative approach. A comparative study involves, by definition, more than one case. It can be conducted over one same subject, as in this research: prostate specific antigen tests in the Netherlands and in the United States of America. By comparing these two countries the results of this research can be put into a wider context. It will also contribute to the production of further information and new knowledge (Grix, 2004).

This research contains the following phases:

1. Identification of a theoretical framework. A desk research will be performed whereby a model operating on different levels is used as a scientific framework for the empirical research. The development and introduction of PSA tests, and POCT tests in a broader context, can be described using this theoretical framework.
2. Identification of the case. A desk research and interviews will be performed to identify the field of point of care tests. Using this information the focus of this research, can be chosen. Then central research questions are formulated. These questions form the basis to examine the situations concerning prostate specific antigen tests in both countries.

3. Identification of the situations in the United States of America and in the Netherlands. A field research will be performed to identify the use of prostate specific antigen tests in America and in the Netherlands. Different target groups will be visited and interviewed.
4. Conclusion. The results of the field research will be compared to each other and put into wider context using the theoretical framework. The conclusions, limitations and discussions will also be mentioned.

3. Prostate cancer

Cancer is death cause number one amongst men in the United States of America (US) and in the Netherlands (NL) nowadays. Next to skin cancer in the US and lung cancer in the Netherlands, prostate cancer has the highest death rates (CBS, 2006; SEER, 2007). In 2004 approximately 7900 men in the Netherlands were diagnosed with prostate cancer (98/100.000 men in NL (RIVM, 2007) and 168/100.000 men in the US (SEER, 2007))

3.1 Benign prostatic hyperplasia (BPH) versus prostate cancer

A frequent need to urinate, inability to urinate, weak urine stream, blood in urine and pain or stiffness in the lower back or hips are all symptoms of prostate cancer. Nevertheless they are also the symptoms of benign prostatic hyperplasia (BPH). So how can you tell the difference? BPH is a benign, or harmless, enlargement of the prostate and is fairly common among elder men (NCI, 2005; PCF, 2005). Benign tumors or enlargements are rarely life threatening and do not spread to other parts of the body. Prostate cancer on the other hand is a malignant, or harmful, enlargement of the prostate. Malignant tumors can be life threatening, and they can metastasize (spread) to other parts of the body (NCI, 2005).

The prostate is a gland found only in men, and can be localized in front of the rectum just below the bladder (see figure 3.1). The prostate produces some of the seminal fluid that transports sperm. When the prostate is enlarged the urethra, which passes the prostate, can become oppressed (NCI, 2005; PCF, 2005).

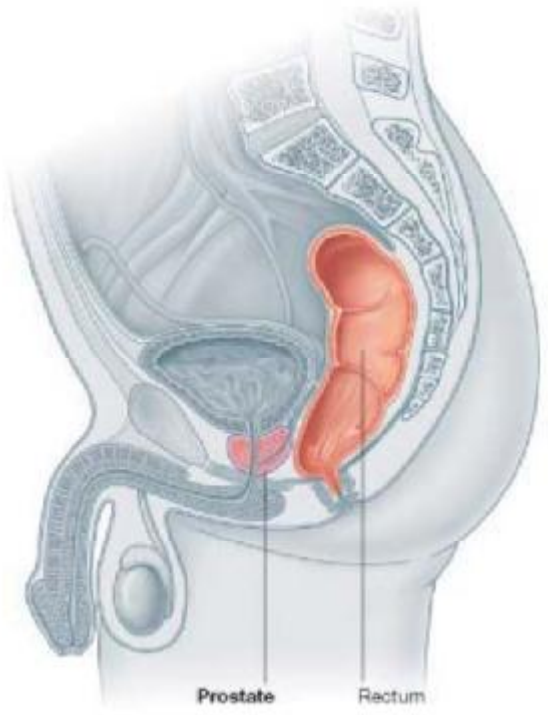


Figure 3.1 Location of the prostate (Drake).

3.2 Prostate cancer detection

When a men, or his physician, suspects either BPH or prostate cancer a number of technologies can be used to detect abnormalities. The most common diagnostic tool is the digital rectal exam (DRE). By inserting his finger into the rectum, the physician checks the prostate gland for areas of irregularity or

hardness. Abnormalities of the prostate gland might indicate prostate cancer. Next to the DRE a blood test is performed, which is called the prostate specific antigen (PSA) test. For this test a small sample of blood is taken and examined by the medical laboratory on the presence of PSA. PSA is a substance not normally found in the blood stream, of which a part is bound to proteins and a part is not, 'free' PSA (Beckman Coulter, 2008).

A follow up test is recommended by the physician when the PSA level is higher than normal, > 2-3 ng/ml (Prostaat.nl, 2008), and/or if the DRE revealed abnormalities. If the PSA level is higher than normal, but the DRE did not reveal any abnormalities, a 'free' PSA test is performed. The percentage 'free' PSA of the total PSA is measured; the higher the percentage of 'free' PSA compared to the total PSA, the less likely the chances of it being prostate cancer (Beckman Coulter, 2008). Except for the total PSA and the 'free' PSA, there are various other parameters which can be used using a PSA test; the PSA velocity, which is an absolute increase of PSA concentration in the blood stream over a period of time. Examples are the PSA doubling time, which measures the time it took for the PSA concentration to double the amount from the starting point; and the PSA density, which is higher in large prostates (Prostaat.nl, 2008).

Next to the 'free' PSA test, a biopsy is a frequently used follow up test. For this a sample of the prostate tissue is examined under a microscope for abnormal cell growth (or cancer). The tissue will be retrieved from the patient using a transrectal ultrasound (TRUS) to locate the exact location of the prostate gland. The samples are then examined by a pathologist, who can also tell the stage of the cancer when present (Beckman Coulter, 2008). In table 3.2 an overview of the stages of prostate cancer is provided. Possible metastasis can be located using an isotope scan of the bones, a CT scan of lymph nodes or using MRI (Prostaat.nl, 2008).

Stage of cancer	Definition
I	The cancer cannot be felt during a DRE. It is found by chance when surgery is done for another reason, usually for BPH. The cancer is only in the prostate.
II	The cancer is more advanced, but it has not spread outside the prostate.
III	The cancer has spread outside the prostate. It may be in the seminal vesicles. It has not spread to the lymph nodes.
IV	The cancer may be in nearby muscles and organs (beyond the seminal vesicles). It may have spread to the lymph nodes. It may have spread to other parts of the body.

Recurrent cancer	The cancer has come back after a time when it could not be detected. It may recur in or near the prostate. Or it may recur in any other part of the body, such as the bones.

Table 3.2 Stages of prostate cancer according to the National Cancer Institute (2005).

3.3 Treatment of prostate cancer

When the diagnosis prostate cancer is drawn up, treatment follows. An operation, radiation therapy, hormonal therapy and chemotherapy are the most used treatments for any stage of prostate cancer, sometimes treatment options are combined.

3.3.1 Surgery

For prostate cancer, surgery is the most common treatment. The surgeon will remove the whole prostate or just a part of it. The removal of the whole prostate is called a radical prostatectomy and can be performed retro pubic, with an incision in the abdomen, or perineal, through the scrotum and the anus. Removing a part of the prostate is usually done with a long, thin device that is inserted via the urethra. This treatment is called the transurethral resection of the prostate (TURP). The surgeon will generally try to use a nerve sparring surgery, which reduces the risk of incontinence impotence (NCI, 2005; RIVM, 2007a).

3.3.2 Radiation therapy

Radiation therapy is sometimes used in prostate cancer instead of surgery. It can also be used as an addition to surgery, in order to remove small remaining parts of the tumor. Radiation therapy can be divided into two different types, external and internal radiation. Some men will receive both therapies. External radiation therapy is the most common sort. Men get treated inside a hospital using a radiation machine. Treatment usually takes five days a week for a period of several weeks. When being treated with internal radiation therapy, the patient gets radioactive material, seeds, inserted into the prostate tissue. The seeds give off radiation for months and are harmless, and therefore do not have to be removed (NCI, 2005; RIVM, 2007a).

3.3.3 Hormonal therapy

The prostate tumor needs male hormones to grow, which are blocked using hormonal therapy. This treatment consist of either drugs or surgery. Different drugs can block male hormones, some can prevent testicles or the adrenal gland from making testosterone, and some can block the action of male hormones. The testicles could also be removed surgically, which is called orchiectomy. Hormonal therapy is mostly used when there is (nearly) no chance on complete recovery (NCI, 2005; RIVM, 2007a).

3.3.4 Chemotherapy

Chemotherapy is mostly used when the cancer has spread outside the prostate and into other parts of the body, such as the bones or lymph nodes. It is applied to shrink the cancer or slow its growth and reduce pain. Chemotherapy consists of anticancer drugs that are injected into the body through a vein, through a muscle or taken by mouth. This drug is known to kill cancer cells, but it will also damage healthy cells. This treatment is, therefore, one of the last options in order to beat prostate cancer (American Cancer Society, 2005). In the Netherlands this treatment option is thought to be little effective and is therefore not often used (RIVM, 2007).

3.3.5 No therapy

The patient or physician can also choose not to undergo therapy. When this is the case most doctors advise 'watchful waiting', or 'active surveillance' (PCF, 2005). Watchful waiting means monitoring the disease in order to avoid or delay the side effects of surgery or radiation therapy (NCI, 2005). It is mostly advised in men with very early stage prostate cancer, men older than the age of 65, and men with co morbidity (PCF, 2005).

3.4 Risk factors

The causes of prostate cancer are not yet fully understood. However, according to the American National Cancer Institute (2005), the Dutch RIVM (2007) and Beckman Coulter (2008), there are several risk factors that can increase the chances of getting prostate cancer.

a) The main risk factor of prostate cancer is age. Prostate cancer is rare in men younger than 45 years. Roughly two thirds of all men with prostate cancer are over 65 years. The older a men is, the bigger are his chances of developing prostate cancer.
b) Family history is said to be the second most important risk factor. When a man has a father, brother or son with prostate cancer, he is more likely to get prostate cancer. In the Netherland 400 families are known to have hereditary prostate cancer (RIVM, 2007).

c) Prostate cancer is more common in black men, they are also twice as likely to die of prostate cancer as white men. Prostate cancer is less common in Asian men. Ethnicity and nationality are therefore thought to be a risk factor (Whittemore, Wu, & Kolonel, 1995a).

d) Some studies suggest a diet can be one of the risk factors. Men who eat a diet with a lot of red meat and/or high fat dairy products are more likely to develop prostate cancer. Men with such diets are also less likely to eat fewer fruits and vegetables (Whittemore, Kolonel, & Wu, 1995b). These studies, however, are inconclusive (RIVM, 2007).

e) The role of male hormones as a risk factor of prostate cancer is still uncertain. According to the RIVM (2007) the association is likely to be a right one, because prostate tumors are dependent of hormones to grow. There is also no known prostate cancer case in men with the testicles removed prior to puberty, in which male hormones normally become active.

Recently Swedish researchers found a combination of five genes common in men with prostate cancer. When four or five variants were present, men were more than four times likely to develop prostate cancer. When family history was added, men with five of the six factors were more than nine times more likely to develop this disease. This study is yet to be verified in other countries (CNN.com/health, 2008).

4. Introduction of PSA test and PSA screening in the American (US) health care sector

Prostate cancer is used in this research as a focus to examine the development and introduction of the broader subject of point of care tests in the Netherlands. Because the development and introduction concerning prostate cancer, and its accompanying diagnostic tools or point of care tests, is in a further stage in the United States of America than in the Netherlands, first the situation in the US will be looked more closely.

In this chapter epidemiological data and noticeable epidemiological trends of prostate cancer in the US are outlined in the first paragraph. In paragraph 4.2 the diagnostics and treatment of prostate cancer in the US are outlined for the period 1975 1988, prior to the introduction of the PSA test. Paragraph 4.3 shows the development and introduction of the PSA test in the US. In this paragraph questions concerning the discovery of PSA and the development of the test are answered, as well as the introduction of the PSA test in the American health care sector. The PSA test can be used in different ways, e.g. it can be used as a diagnostic tool, as a monitoring tool and as a screening tool, which will be explained in the fourth paragraph. The development and the introduction of PSA screening in the US is the main subject of this paragraph. In the last paragraph all findings described in chapter 4 will be summarized in the multi level model discussed in the second chapter.

4.1 Epidemiological data of prostate cancer in the United States of America

Approximately 2.024.489 men had prostate cancer in the United States of America in 2004 (SEER, 2007). The total number of cases of a disease in a given population at a specific time can be considered the prevalence. The incidence rate at that time was 168,0 per 100.000 men. Incidence means the extent or rate of occurrence, especially the number of new cases of a disease in a population over a period of time. For prostate cancer this means that 168 men out of 100.000 were newly diagnosed with prostate cancer in 2004. The mortality rate, also known as the death rate, was 27,9 per 100.000 men. Recent literature, such as Whittemore et al. (1995a; 1995b), Hankey et al. (1999) and even more recent Dennis & Resnick (2000), demonstrate significant differences of prostate cancer incidence among ethnic groups. In table 4.1 the incidence rate, the prevalence and the mortality rate is split up for the different ethnic backgrounds of American men. Statistic data (SEER, 2007) verifies significant differences in ethnics; [1] black men have a higher incidence rate than white men, [2] Asian men have a lower incidence rate than white men, and [3] black men have the highest mortality rate. Although these numbers seem factual, we have to take into account that these statistics are a few years old and can consequently not be seen as absolute numbers. These statistics have to be seen as estimations. The

American Cancer Society (ACS) estimated that 218.890 men will be newly diagnosed with prostate cancer in 2007, and 27.050 men will die of this disease (ACS, 2007). The real numbers are yet to be published.

Ethnics	Incidence rate*	Prevalence	Mortality rate*
All races	168,0	2.024.489	27,9
White	161,4	1.726.588	25,6
Black	255,5	236.425	62,3
Asian/Pacific Islander	96,5	**	11,3
American Indian/Alaska Native	68,2	**	21,5
Hispanic	140,8	**	21,2

Table 4.1 US incidence, prevalence and mortality rate in 2004 (SEER, 2007). *per 100.000 men; ** missing data

4.1.1 Trends in US incidence

Incidence, prevalence and mortality rates are only interesting if a trend can be seen. In order to detect these possible trends in for example the incidence rate, several years must be compared. In figure 4.2 all known incidences are given for the period 1975-2004. The Surveillance Epidemiology and End Results (SEER) uses the annual percentage change (APC) for information concerning trends over a fixed period of time. The SEER is part of the US National Cancer Institute, and provides all national cancer statistics.

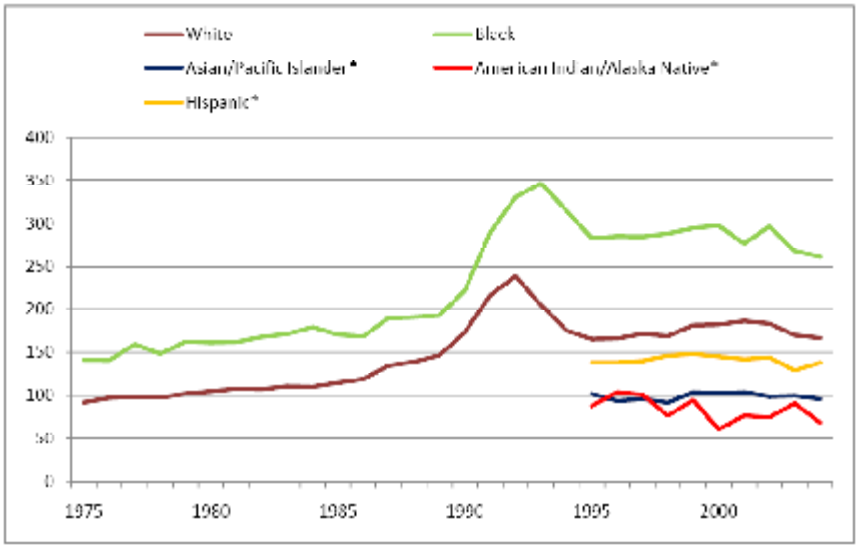


Figure 4.2 US incidence rate per 100.000 men (SEER, 2007). * *Incidence data not available before 1995.*

In figure 4.3 the ACP for men of all ages is given. If there is a negative column, the trend is a decrease; otherwise the trend is an increase of the incidence rate. Hankey et al. (1999) described a large increase in incidence of prostate cancer in the early nineties, followed by a peak and eventually a slow decrease. For all races there was an increase of new prostate cancer cases in the period of 1975-2004. In the second period (1995 2004) there was a small decrease, followed by a large decrease in the period 2000 2004. These findings are consistent with the data retrieved from the SEER incidence data (2007).

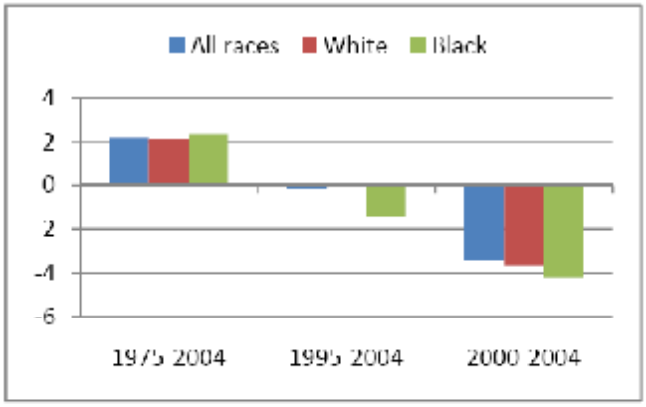


Figure 4.3 Trend of US prostate cancer incidence for all men (SEER, 2007).

Hankey et al. (1999) also demonstrate more men were diagnosed at an early age. In order to see if this is consistent with the data retrieved from the SEER incidence data (2007) we split the incidence data to age; for men younger than 50 years and men older than 65 years.

According to figure 4.4 there was a large increase in new prostate cancer cases among men younger than 50 in all races. In the next two periods this increase declines. This means in the first period more men younger than 50 were diagnosed with prostate cancer than the years prior to this. In figure 4.5 a small increase of prostate cancer incidence was found in men older than 65 years in all races. In the last period, 2000 2004, there was a large decrease of new found prostate cancer cases.

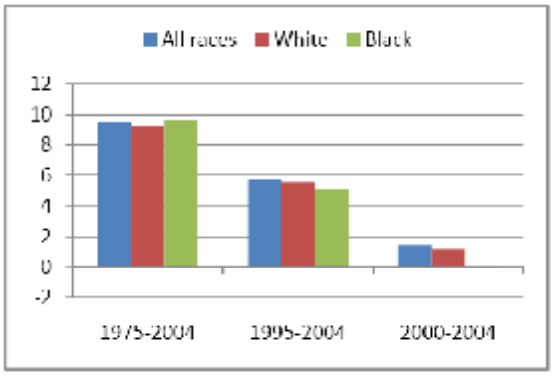


Figure 4.4 Trend of US prostate cancer incidence for men <50 years (SEER, 2007).

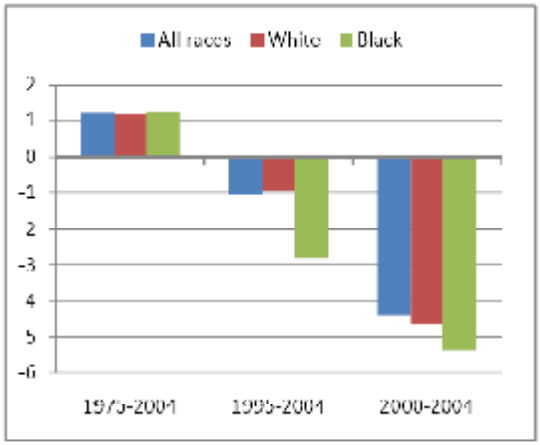


Figure 4.5 Trend of US prostate cancer incidence for men >65 years (SEER, 2007).

Concluding we could say that in the last years more men under the age of 50 are diagnosed with prostate cancer, and less men above the age of 65, which is consistent with literature found (Hankey, et al., 1999; Dennis & Resnick, 2000).

4.1.2 Trends in stages

Next to the trend towards more detected cases of prostate cancer in the last decades and at a younger age, there is also a trend in different stages in which the prostate cancer is first diagnosed. In the third chapter about prostate cancer an overview is given for the different stages of prostate cancer. In figure 4.6 these four stages are combined into [1] localized, which means the cancer has not spread outside the prostate (stage I and II), and into [2] distant, which means the cancer has spread outside the prostate (stage III and IV). There is also a column with [3] unstaged prostate cancer, this is prostate cancer which was not staged at the time of discovery.

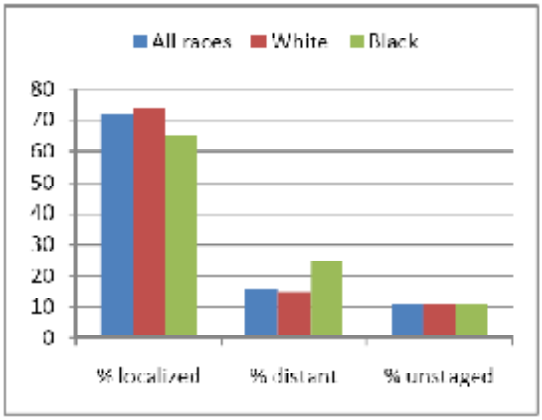


Figure 4.6a Stages of prostate cancer 1988-1989 (SEER, 2007).

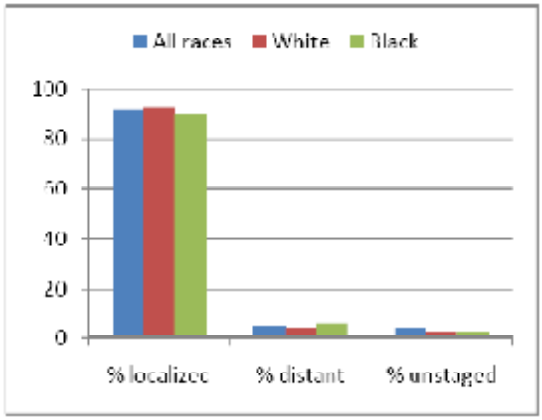


Figure 4.6b Stages of prostate cancer 1998-2004 (SEER, 2007).

According to the SEER incidence date (2007) 72% of men diagnosed with prostate cancer, were staged as localized in 1985 1989. In the period of 1996 2003 this percentage was 92%; an increase of 20%. Nearly 16% of men diagnosed with prostate cancer in the period 1985 1989 were diagnosed with a distant stage, in contrast to less than 5% in the period 1996-2003; a decrease of nearly 10%. Furthermore a shrinkage of the number of unstaged patients is noticeable. In accordance with literature found (Hankey, et al., 1999; Dennis & Resnick, 2000) and the SEER incidence data (2007) we can conclude there was a shift towards the detection of a more early stage prostate cancer.

4.1.3 Conclusion

In literature and data retrieved from Surveillance Epidemiology and End Results (SEER) we found three main trends concerning prostate cancer. First the trend of the US prostate cancer incidence rate, which can be divided into three periods 1975 1995, 1995 2000 and 2000 2004. In the first period there was a large increase, first followed by a peak and later by a decrease of incidence. Second a trend is seen in the age of men diagnosed with prostate cancer. In the last decades more men younger than 50 years were diagnosed and less men older than 65 years. However, we must take note of the fact that, although the trend of more men being diagnosed at a young age was seen, the effect is currently declining. In the last periods less men younger than 50 years were diagnosed than in the first period. For the age group of men older than 65 years of age, this fact does not apply. The number of men older than 65 years diagnosed with prostate cancer is increasing even more as years go by. The third trend is the stage in which prostate cancer is found in patients, when they are first diagnosed. In the two periods examined an increase of 20% in early stage (I and II) prostate cancer was found and a 10% decrease of late stage (III and IV). These trends lead to questions concerning the way of development of practices of detection and treatment of prostate cancer in the US in the course of time. In the remaining of this chapter these questions will be addressed and answered.

4.2 Diagnostics and treatment of prostate cancer in the United States of America

The first people on earth died at a fairly young age due to different sorts of illnesses and other threats. Because of improved medical care, among others, overall life expectancy has improved a lot. With this improvement, new diseases, such as cancer, have emerged. Prostate cancer is one type of cancer that has emerged with a prolonged life expectancy, also due to the fact prostate cancer has only been seen in older men so far. In the period prior to the discovery of the PSA test, 1975 until 1988, prostate cancer was also diagnosed, but in a different way as described in chapter 3. In this section an overview is given of the practice of diagnostics and treatment of prostate cancer as it was prior to the introduction of the PSA test.

US practice (1975-1988)

When a men had urinary problems, such as being unable to urinate, he would consult a physician. The physician would then take a history to find out the background of the symptoms of his patient. Questions such as the seriousness and the duration of the symptoms, as well as family history, are answered by the patient. If the physician would then suspect a condition such as BPH or prostate cancer, he would perform a diagnostic test called the digital rectal exam (DRE), which is to detect possible irregularities or hardness of the prostate. If something abnormal was found during the DRE, a small tissue sample (biopt) was taken from the prostate and looked at using a microscope (NCI, 2005). In the serum of prostate cancer patients an prostatic acid phosphatase (PAP) was found in 1938. The presence of this PAP was looked at using a microscope and used as a prostate cancer diagnostic tool (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007). In this period the average prevalence of prostate cancer was approximately 1.105.124 men (SEER, 2007). As mentioned in the first paragraph of this chapter, approximately 72% of prostate cancer found in this period was categorized as stage I or stage II (early stage) prostate cancer, 16% was diagnosed with advanced stage cancer (stage III or IV) and the remaining 11% was not staged at the time of discovery (SEER, 2007).

If prostate cancer was diagnosed, treatment followed. In the period prior to the introduction of the PSA test, a physician could choose between two treatment options, surgery or radiation therapy. Surgery as a treatment option comes down to the removal of (a part of) the prostate. This treatment has a lot of side effects, such as incontinence and impotence. Radiation therapy was mainly used as an addition to surgery, but sometimes as a treatment on its own. Radiation therapy kills the malignant cells, but it also harms healthy cells.

The prognoses of men diagnosed with prostate cancer in this period, depended on different factors, such as the stage of the prostate cancer. Men with an early stage prostate cancer had nearly 94% chance on surviving the first five years after the date of diagnosis, and 90% chance of surviving the first ten years. Only 57% of men diagnosed with advanced stage prostate cancer survived the first five years, and 51% the first ten years. Men in whom the prostate cancer was not staged, 86% survived the first five years, and 82% the first ten years (SEER, 2007). Looking at these numbers it is likely to say there were more early stage cancer cases in the unstaged group than advanced stage. Men with early stage prostate cancer had a better prognosis than men with an advanced stage cancer.

Figure 4.7 Practice of diagnostics and treatment of prostate cancer (1975-1988)

Although a lot of men survived the first five or ten years after being diagnosed with prostate cancer, a lot of men died of prostate cancer. In the period prior to the introduction of the PSA test, 1975 1988, approximately 333.910 men died due to prostate cancer. When these numbers are split into different races, we see that twice as much black men died of prostate cancer than white men in the US in this period.

4.3 Development and introduction of the PSA test in the United States of America

The prostate specific antigen (PSA) test is a widely used test in the United States of America, but how does it work and when was it discovered? The answers to these questions will be provided in this paragraph.

4.3.1 Discovery of PSA

In 1966 antigens, which are substances that can stimulate the production of antibodies, specific to the prostate tissue were characterized. Hara and a few of his Japanese colleagues identified gamma seminoprotein (γ-SM), a prostate specific protein, in 1974. An assay that could detect this protein was developed and used for forensic purposes. The expectations of this assay, and subsequently of this protein, was that it could detect the presence of seminal fluid in rape cases (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007). Wang et al. thought both substances found, the antigen found in 1966 and the γ-SM found a few years later, to be the same.

Research showed Wang et al. were right and gave the substance a new name; prostate specific antigens (Makarov & Carter, 2006). They also found out that prostate specific antigens were prostate centralized, and could therefore not be detected in other parts of the body. Research around the origin of these antigens continued; researchers Chu, Wang, Papsidero and colleagues at Roswell Park Cancer Institute in Buffalo, New York found out in 1992 that all the prostate specific antigens have the same amino acid sequences, therefore

they all originate from the same gene. After these findings, the substances called prostate specific antigens became known as prostate specific antigen, also known as PSA (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007).

Since 1938 PAP was used to diagnose prostate cancer, research showed that PSA and PAP were two different substances, both immunologically and chemically (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007). Stamey et al. conducted a research on the differences between PSA and PAP and concluded that [1] PSA was a more sensitive marker for prostate cancer, [2] PSA levels increased directly with the stage of the cancer, [3] PSA decreased to undetectable levels after surgical removal of the prostate, and [4] PSA appeared useful for detecting residual disease after treatment (Stamey, Yang, Hay, McNeal, Freiha, & Redwine, 2006). Researchers and medical professionals had high expectations of the possibility of detecting this new substance, and thought it was the best possible way to diagnose prostate cancer. The PSA test was the first test discovered to have a high sensitivity in the detection of prostate cancer.

Researchers and medical professionals thought all prostate cancer patients could be diagnosed by only using this, relatively easy to perform, blood test. PSA is not normally found in other parts of the body, such as blood, except in the prostate. If high levels of PSA is produced by the prostate, e.g. in cases of prostate illness, a part of the PSA will go into the blood stream, where it can be detected using a PSA test. However, in 1988 the first PSA test was not introduced for diagnostics, but as a monitoring tool.

4.3.2 Introduction of PSA test in 1988

In 1986 researchers put in a request for the approval of the first PSA test at the US Food and Drug Administration (FDA), one of the public health service agencies of the US Department of Health and Human Services. The PSA test was approved by the FDA in 1986 to "*aid in the care of patients who already had been diagnosed with prostate cancer*" (FDA, 1994). The first PSA test was therefore introduced to the market as a monitoring tool, which could track the progress of the disease after treatment (Makarov & Carter, 2006). Medical professionals used the PSA test to detect residuals of prostate cancer after they had performed treatment. The PSA test was also used to monitor the recurrence of the cancer in treated prostate cancer patients.

Meanwhile clinical trials were performed to determine the possibility of using the PSA test as a diagnostic tool. In 1994 the Food and Drug Administration (FDA) approved the first PSA test used to detect prostate cancer in men 50 years and older. The test was only approved in combination with a digital rectal exam (DRE). The FDA believes "*the PSA test by itself cannot be relied on to determine whether a man has prostate cancer. It must be*

used in conjunction with other diagnostic procedures, including the digital rectal exam. The final diagnosis requires a biopsy" (FDA, 1994).

4.3.3 US practice (1988 and further)

Medical specialists first were reserved with the approval of the PSA test being used as a way to detect prostate cancer. However, several high quality clinical studies validated the PSA test, through which medical specialist started using the PSA test more frequently. After all, in the early nineties, prostate cancer was the second most common cancer found in men (FDA, 1994). Hence medical specialist used the PSA test more regularly, as could be seen in the first paragraph of this chapter.

Improved treatment options also contributed to the widely adaption of the PSA test in the US practice in 1988 present. In the early 1980's Walsh developed the so called nerve sparring prostatectomy. In the previous way of performing a prostatectomy, nerves, which protects a man from being incontinence and/or impotence, were frequently harmed. With this new nerve sparring prostatectomy, the prostate gland could be removed without these negative side effects.

However, researchers warned users of the PSA test that elevated levels of PSA often occurs in other prostatic illnesses, such as benign prostatic hyperplasia (BPH). The FDA also states in the approval that "*while high levels of PSA may signal prostate cancer, they may also signal other common, non-cancerous prostate disorders. Conversely, low PSA levels do not necessarily indicate an absence of prostate cancer. Therefore, it is important that the PSA test be interpreted with results from other established procedures such as a digital rectal exam. If either test is positive, confirmatory testing with transrectal ultrasound (TRUS) and biopsy is needed to diagnose prostate cancer*. (FDA, 1994)"

As showed in sector 4.1.2 more men were diagnosed at an early stage in the late 1990's, which was mostly ascribed to increased use of the PSA test (NCI, 2005). On the other hand lowering the cutoff point[1] of the PSA test could also have contributed to a more early diagnosis of prostate cancer. In 1986 a large study was performed by one of the developers of the PSA test, Hybritech Inc., to determine the cutoff point for prostate cancer. Prior to this study a cutoff point of 10 ng/mL was used to determine the means of biopsy in prostate cancer. This study showed that in men with PSA levels higher than 2.8 ng/mL prostate cancer could be found. But because other studies showed a cutoff point of 4.0 ng/mL was significant enough, this became established for recommending biopsy. Recent studies however, have shown that many cases have been missed with this cutoff. Therefore the cutoff point was recently lowered again. The 2.5 ng/mL cutoff point is recently

[1] Cutoff point: a point serving as the limit beyond which something is no longer effective, applicable, or possible.

recommended by the National Comprehensive Cancer Network (NCCN) in the United States (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007).

In the approval of the PSA test as a diagnostic tool, FDA Commissioner and doctor D.A. Kessler said "*This test, used with other procedures, can help detect those men at risk for prostate cancer early on when more treatment options are available. But for the test to help, men must be aware of the importance of early check-ups and get them on a regular basis* (FDA, 1994)." This quote was one of the factors that started the beginning of prostate cancer screening, as will be attended to in the next paragraph.

4.4 Development and introduction of PSA screening in the United States of America

As discussed in previous paragraphs the PSA test can be used to monitor or detect prostate cancer, but it can also be used to screen for the presence of prostate cancer. Even before any symptoms are noticeable. In this paragraph an overview of the development and introduction of PSA screening in the US is outlined.

4.4.1 Development of PSA screening in the US

PSA screening uses the same technology as is used in monitoring and detecting prostate cancer; the PSA test. Therefore in this sector the social development of PSA screening will be addressed, instead of the technological development. Since the introduction of the PSA test in the US in the 1980's, many experts stated strongly that PSA would not be useful for the application of prostate cancer screening (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007). However nowadays PSA screening is used on large scale in the American health care sector.

The major reason experts in the 1980's were convinced the PSA test would not be useful for prostate cancer screening, was the lack of sensitivity of the test (Angelis, Rittenhouse, Mikolajczyk, Shamel, & Semjonow, 2007). The PSA test does not distinguish between prostate cancer and BPH, as was explained in the third chapter of this report. The PSA test has false positive test results and false negative test results. False positive test results mean there is an elevated PSA level, but no cancer is present. In this case it is most likely the patient has BPH. False positive results may lead to unnecessary treatment and can create anxiety. False negative test results mean the test shows low PSA levels, but cancer is present (NCI, 2007). At a level 4.0 ng/mL the positive predictive value of 26% (sensitivity 44%, specificity 94%) can be reached, but two thirds of cancers can also be missed (Price, St. John, & Hicks, 2004).

In health care a distinction is made between different means of screening; individually and mass screening. Individual screening means screening one person to benefit only this person. Individual screening is often

performed on request of the patient or his physician. Mass screening is regular screening through, for example, national screening programs. All men in a certain risk group are requested to perform a test, however, this test is voluntarily. The results of these programs will not only be used for the individual screened, but also for epidemiological purposes. In this report both definitions of screening will be used.

4.4.2 Introduction of PSA screening in the US

Despite the negative first reaction to PSA screening, it was introduced gradually in the US over several years. In the United States of America all inhabitants, with an insurance, are required to get an annual physical. During this yearly check-up, patients are screened for numerous illnesses to determine if they are still healthy. With the introduction of the PSA test in 1988 it became relatively easy to monitor, detect and even screen for prostate cancer. Although the PSA test was not approved for screening purposes at first, physicians saw the benefits of early detection of prostate cancer and started individual PSA screening. During the introduction process of PSA screening, a lot of discussions and debates concerning several aspects of using the PSA test for screening purposes arose. The major topics[2] can be described as following:

- At first, physicians were allowed by the FDA to use PSA tests to individually screen men with a high risk of getting prostate cancer. These are men older than 65 years, men who have family history of prostate cancer and men with certain ethnic backgrounds. Due to patients anxiety for the chances of developing prostate cancer, and due to the emerging culture of lawsuits, more physicians started to screen men for the presence of prostate cancer. Offering the PSA test as a (individual) screening method allowed a shift to happen towards more men being screened. Men of the age of 50 and older are being screened, and men with a family history as well as men without (ACS, 2003). This shift towards over screening, which means screening men who are not at high risk, has also been encouraged by insurance agencies, who demand frequent check ups. By demanding these check ups insurance agencies try to detect diseases at an early stage, to avoid major costs that could have been prevented.
- Because of the low sensitivity of the PSA test, more men are being diagnosed with prostate cancer using PSA screening, than necessary. As stated before the PSA test does not distinguish between BPH and prostate cancer. When the test is positive, and a patient is diagnose with prostate cancer, it does not always mean he really has prostate cancer. He could also have elevated PSA levels due to BPH. Therefore, due to a low sensitivity, over diagnosing is another side effect of PSA screening. Over-

[2] All these topics are still being discussed as research is still being performed. No unambiguous results have been reported yet.

diagnosing means diagnosing tumors that would otherwise remain clinically unrecognized until the individual died from other causes. Research is still being performed and mass screening trials are being evaluated. But with one time screening, a recent Swedish study (Hugosson, et al., 2000) has shown, under-diagnosing is the case rather than over-diagnosis.

- Although the sensitivity of the test has not increased over the last years, PSA tests are being used for prostate cancer screening. Due to the low sensitivity of the test, patients with BPH are treated as if they have prostate cancer, while they might not even need treatment at all. Invasive treatment of tumors that would unlikely to be harmful, is called over treatment. A Canadian study (McGregor, Hanley, Boivin, & McLean, 1998) estimated the magnitude of over-detection of prostate cancer using screening. They found only 16% of men diagnosed with prostate cancer through screening benefit from treatment. This means when 100 men are treated, only 16 men will benefit of this. However, some of the leading researchers, developers and users of PSA screening say it is better to treat too much patients than too little.
- A positive effect of PSA screening is the declined mortality rate seen since the introduction of the PSA test. Many experts expect the mortality rate to decline even further, as more treatment options are available for early stage prostate cancer. They also espect screening for prostate cancer will lead to more early stage cases. Weinmann et al. (2004) show, in a recent study, that men who have been screened for prostate cancer have a reduced risk of dying of this disease. In this research no difference has been made between prostate screening using DRE or PSA. Therefore the outcomes of this study are only for screening for prostate cancer using both screening methods. However, in a review on PSA testing, physician Albertsen (2006) states two large randomized trials are currently in progress to examine whether or not mortality risk declines. Their results have yet to be published, therefore a statement cannot be made according to Albertsen.

4.4.3 Public debates concerning PSA screening in the US

Debates about PSA testing concern different subjects, such as national screening, over screening, over-diagnosing and over treating men, and the sensitivity and specificity of the tests.

In a study about cancer screening held in 2001 and 2002, 87% of the respondents believe routine screening of cancer is 'almost always a good idea'. Researchers believe there is a desire for early detection of cancers, because 74% of the individuals think finding a cancer early saves lives. 53% believe screening usually reduces the amount of treatment needed when cancer is found. Two thirds of the interviewees would want to be tested for a cancer, even though nothing could be done about the disease (Schwartz, Woloshin, Fowler, &

Welch, 2004). However, scientists are not sure mass screening is an option, because of the threat of over screening, over diagnosing and over treating men.

Interviews

During the research period in San Francisco, CA, USA, different actors concerning prostate cancer and PSA tests were interviewed. Only a few of them will be mentioned in this research; Dr. Peter Carroll, an urology oncologist and chair of urology at UCSF Medical Center and Stan Rosenfeld, a prostate cancer survivor and UCSF Medical Center Prostate Cancer Advocate in Marin County, CA, USA.

Dr. Peter Carroll, one of the leading prostate cancer surgeons in the U.S., says many man with early stage prostate cancers may be undergoing unnecessary treatment. "*About half of the men being treated for prostate cancer have low-risk disease, and some of these men may never need treatment*" says Dr. Carroll. Many men will live their lives never having any symptoms. Carroll says "*unlike with many other cancers, among men with prostate cancer there is a significant reservoir of silent disease that is destined to remain silent*." He also mentions that prostate tumors are being detected at a lower grade and smaller size on average than a decade ago. Most of these tumors are treated by performing a radical prostatectomy or radiation therapy. Such treatments can result in impotence, urinary incontinence or other side effects (Carroll P. , 2007).

Stan Rosenfeld looks after the opinion of all men diagnosed with prostate cancer in the San Francisco Bay Area region. He says "*to me, that flies in the face of every patient saved. If it came to be that we unnecessarily need to treat men, even if it is a large number of men, to save an even larger number of men, that was the right thing to do!*" (Rosenfeld, 2007)

There is also a lot of discussion about the effectiveness, and accuracy, of the PSA test, because a distinction between benign (not harmful) and malignant (harmful) cannot be made using a PSA test. Prof. Dr. Stamey, who was one of the first to introduce and use PSA testing in the United States of America, first was very enthusiastic (Stamey, Yang, Hay, McNeal, Freiha, & Redwine, 2006), but is now backing out of his statement PSA is the best way to diagnose prostate cancer. He believes more research should be done to find other, better, ways to detect prostate cancer. (Rosenfeld, 2007)

4.4.4 Public policy of PSA screening in the US

Discussions concerning these major topics have led to several recommendations and guidelines from governmental and professional organizations concerning PSA screening. However these recommendations and guidelines have conflicted over time. The US Preventive Services Task Force (Voss & Schectman, 2001), the American College of Physicians (Voss & Schectman, 2001) and the American College of Preventive Medicine (Ferrini, Steven, & Woolf, 1998) have stated there is a lack of evidence that supports PSA screening. The

American Urological Association (Ferrini, Steven, & Woolf, 1998) and the American College of Radiology however, recommend annual DRE and PSA screening for high risk patients (Ferrini, Steven, & Woolf, 1998). The American Cancer Society (ACS) has been a major advocate of the use of PSA screening in the last years. However, the ACS is altering their opinion. The ACS now states "*the PSA test and DRE should be offered annually starting at the age of 50 for men with a life expectancy of at least ten years. Information should also be provided to men about the benefits and limitations of testing so that an informed decision about testing can be made with the clinician's assistance* (ACS, 2003)."

Because of these conflicting recommendations and guidelines, and due to the fact research in regard to the outcomes of (mass) screening is still being performed, there is no national mass PSA screening program for prostate cancer in the US at this moment. Individual prostate cancer screening is, nevertheless, widely performed in the United States of America. Voss and Schectman surveyed 176 physicians in the period of 1993 1998 about the use of PSA tests for screening purposes. The physicians reported high and increased use of PSA tests in men older than 50 years without any symptoms from 1993 to 1998. They were also more enthusiastic towards PSA tests in this period. Physicians state that they perform a test for several reasons, among which are the belief it is standard practice and the fear of getting a lawsuit (Voss & Schectman, 2001).

A study about the influences of patient's anxiety and expectations on decision making shows other reasons why a physician screens for prostate cancer. This research of Haggerty et al. (2005) shows the influence patients have on decision making. Physicians who order a test for screening purposes believe that routine screening was recommended. Physicians who did not thought a routine screening was recommended, performed screening because of patients' expectations (88%) or patients' anxiety (87%).

In the United States of America approximately 75% of all men above 50 years have had a PSA test done as a screening method. Therefore despite the fact screening is not recommended for mass screening, individual screening for prostate cancer is common in the US.

4.4.5 Conclusion

The PSA test as a screening method has been developed and introduced over time. Prior to the introduction of PSA screening, the method used, the PSA test, was questioned. The major concern was the low sensitivity of the test. Despite this concern, individual PSA screening started to become more common. Mass screening was thought to lead to over screening, over diagnosing and over treating of men. Because results of mass screening trials are not yet published, major governmental and professional parties are against screening. Other parties state PSA screening should be offered annually, and are therefore advocates of individual screening.

Physicians perform (individual) PSA screening regularly, as 75% of all men over 50 years in the US has had one done. The anxiety and expectations of patients play a major role in the decision whether or not to screen for prostate cancer. Some physicians believe screening is the recommended practice.

Despite all conflicting recommendations and guidelines, individual PSA screening is common practice in the US. It has acquired its present position in the existing regime of regularly medical check-ups, mainly due to the role of physicians and the annual physicals.

4.5 Conclusion

The practice concerning the detection of prostate cancer in the American health care system has changed over time. In this chapter all major developments were described. Now a conclusion will be drawn using the multi level model described in the second chapter. By molding the conclusion of this chapter, and those of chapters 5 and 6, it is possible to compare these results more efficiently.

In the period 1975 1988 the US regime for detection of prostate cancer was formed by e.g. different guidelines, technologies and social factors. The diagnosis prostate cancer was given when irregularities were found during DRE. Because the procedure of a DRE is considered quite uncomfortable researchers were looking for other detection methods. Also the increasing mortality rate of prostate cancer increased the need for better diagnostic methods.

At niche level researchers were performing studies for different purposes. In 1966 the discovery of PSA started, but it was not until 1988 the first PSA test was ready for introduction. The PSA test merged from the 'niche' level into the existing regime of detecting prostate cancer mainly using DRE.

The test was seen as a promising substitute for DRE and PAP. However, different leading specialist in the area of PSA test warned users for the low sensitivity of the PSA test. They advised physicians to use the PSA test in combination with the DRE. This way, the PSA test was eventually adopted to the existing regime of 1975 1988.

As the use of PSA test increased, more functions of this test became known. Next to the use of PSA test as a monitoring tool and as a diagnostic tool, it could also be used as a screening tool. This understanding began at regime level, as the test was used in this setting. However, it can also be seen as a new 'niche' level in which PSA screening was discovered.

The introduction of PSA screening went different from that of the PSA test. Individual PSA screening was adopted in a different regime of annual physicals and yearly screening for diseases. The existing landscape of lawsuits and insurance agencies have contributed to this relatively easy adoption of individual PSA screening.

Mass screening is not adopted in the US yet, due to several factors at landscape level. The US health care system is formed by different recommendations and guidelines. For mass screening also recommendations and guidelines exists. The PSA screening does not yet meet the criteria's needed for national (mass) screening.

5. Introduction of PSA test and PSA screening in the Dutch (NL) health care sector

The development and introduction of PSA test in the Netherlands is examined in this research. In the previous chapter the situation concerning PSA test in the United States of America is outlined. After evaluating the Dutch situation, a comparison between these countries can be made. This chapter uses the same build up as chapter 4, however the data is tailor made to the Netherlands. On grounds of the description of the developments in the Netherlands, the question, to what extent these developments are comparable to or differ from the developments in the United States of America, can be answered.

5.1 Epidemiological data of prostate cancer in the Netherlands

The number of new prostate cancer cases in 2003 was 7.902, which made prostate cancer the most common form of cancer in men. 21% of men with any form of cancer has prostate cancer. There are approximately 35.800 men diagnosed with prostate cancer in the period 1993 2003. A quick calculation shows that on average 3580 men were diagnosed with prostate cancer yearly in this period. In 2003 this number was twice as high. The reasons for this large difference, amongst others the introduction of PSA tests in the Netherlands, will be addressed to in this chapter. The Netherlands is one of the European countries with the highest incidence and mortality rate of prostate cancer. (NKV, 2007) Table 5.1 shows the comparison between the Netherlands and the United States of America in a practical overview. The incidence rate is almost twice as high in the US than in the Netherlands, however the mortality rate in the Netherlands is higher than in the US. (NKR/IKC, 2007; RIVM, 2007a; SEER, 2007)

	Incidence rate*	Prevalence	Mortality rate*
NL in 2003	98,4	35.800**	29,3
US in 2004	168,0	2.074.489	27,9

Table 5.1 NL and US Incidence, prevalence and mortality rate (NKR/IKC, 2007; RIVM, 2007a; SEER, 2007). * per 100.000 men; ** estimated in 2002

5.1.1 Trends in NL incidence

In the Netherlands, all epidemiological data concerning cancer, is administered by the Integrale Kankercentra (iKC's). The iKC's are integral cancer centers which cover different geographical parts of the Netherlands. The

data of these 9 iKC's are combined in one database, called the Nederlandse Kankerregistratie (NKR), i.e. the Dutch cancer registration. In this paragraph most data is retrieved from this database.

The incidence rate can be looked at over time, as was done with the US incidence rate in the previous chapter. Recent literature, such as Bangma (2002) and Widdershoven et al. (2007), show three periods in the incidence rate can be identified. They say the incidence can be divided into the period until 1992, 1992-1994 and the period starting from 1994. These findings correspond with data found in the NKR. In the period 1989 1992, the mean incidence rate was somewhere around 60 per 100.000 men (see figure 5.2). In 1992, an increase in incidence is noticeable, until 1994, the number of men diagnosed raised to nearly 90 per 100.000 men. A quick calculation shows this is an increase of 41%. After 1994, the number of new cases stabilized for a long time. Only recently the number increases slowly to almost 100 per 100.000 men (NKR/IKC, 2007).

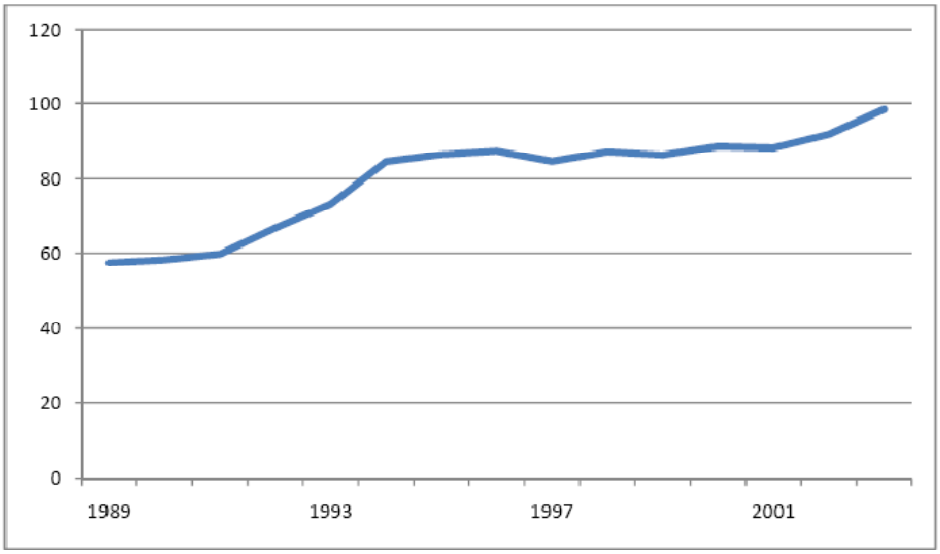


Figure 5.2 NL incidence rate per 100.000 men (NKR/IKC, 2007).

Compared to the United States of America, a few differences can be seen, as showed in table 5.3. In the period from 1989 1992 the US incidence rate increased, while the Dutch incidence rate stayed the same. The Dutch incidence rate started to increase in the period 1992 1994, in this same period the US incidence decreased. The increase in Dutch incidence until 1994 can be ascribed mainly to the use of new diagnostic tools, such as the PSA test. The development and introduction of this test is described in paragraph 5.3 (NKV, 2007). In the following period, 1994 2000, the incidence rate in both countries stayed the same. The most remarkable

difference is the increase of the Dutch incidence rate in the period 2000 2004. In the United States of America, the incidence rate stayed at the same level in this period. The explanation for this difference will be given in the following paragraphs of this chapter.

	United States of America	The Netherlands
1975-1989	—	
1989-1992	↗	—
1992-1994	↘	↗
1994-2000	—	—
2000-2004	—	↗

Table 5.3 NL and US trends in incidence rate (NKR/IKC, 2007; RIVM, 2007a; SEER, 2007).
— flat line; ↗ increase; ↘ decrease

The incidence of prostate cancer is strongly correlated with the age of detection. As shown in figure 5.4 prostate cancer is rarely found in men under the age of 45; starting from 45 the incidence increases a little. The age group 60-74 years had an incidence of 257 per 100.000 men per year in 1989 1992, which increased to 431 per 100.000 men per year in 2000 2003. This means an increase of nearly 70% in a period of 14 years. The highest incidence still is among men who are 75 years and older. The incidence rate started at around 768 per 100.000 men per year in 1989-1992, and is currently at 713 per 100.000 men per year in 2000-2003. This incidence rate has increased a lot at first, but declined just as fast starting from 1994. The total decrease is 7% (NKR/IKC, 2007).

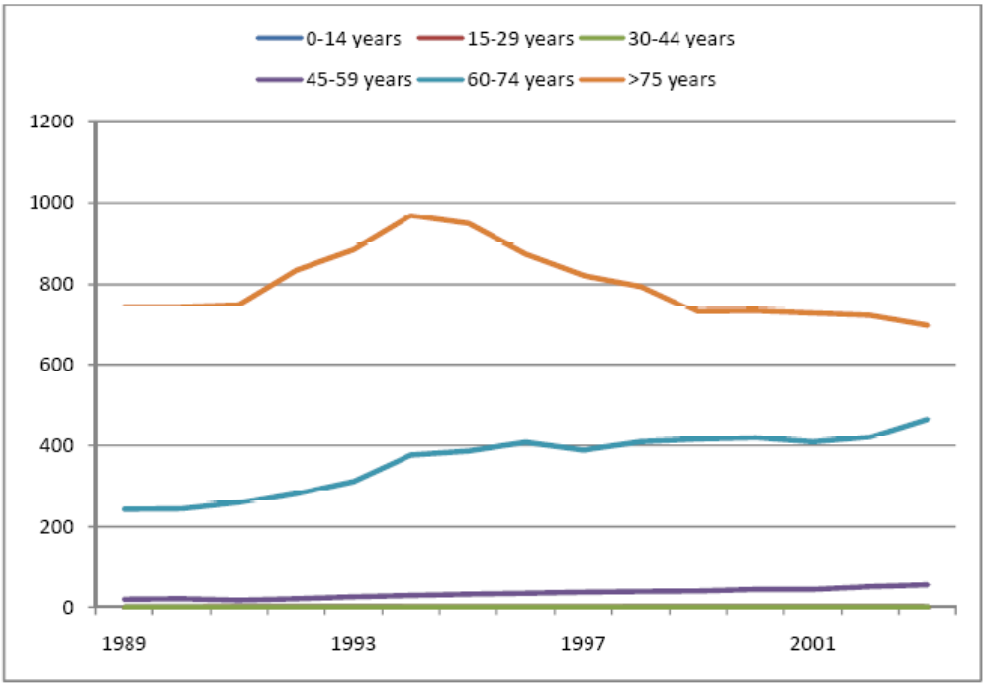


Figure 5.4 Trend of NL prostate cancer incidence per 100.000 men for different age groups (NKR/IKC, 2007).

5.1.2 Trends in stages

In chapter four, a shift in stage distribution over years was noticeable in the US incidence data; the same goes for the Netherlands. Figure 5.5a shows the stage distribution of prostate cancer found in men younger than 70 years for different periods of time. The detection of stage I and II prostate cancer has grown over time, while the detection of stage IV prostate cancer declined. Stage II has stayed more or less the same over the different periods. For the age group of men older than 70 years, the same trend occurs. For both age groups the staging of prostate cancer has improved in the last decades, as can be concluded from the reduction of unknown stage prostate cancer (NKR/IKC, 2007).

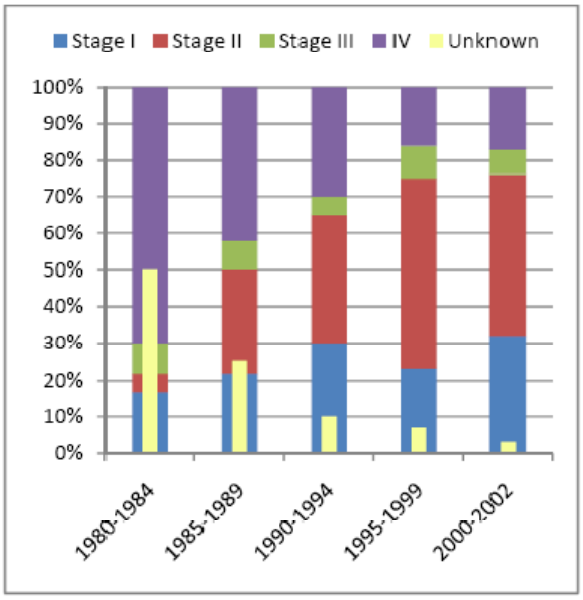


Figure 5.5a Stage of prostate cancer in men <70 years (NKR/IKC, 2007).

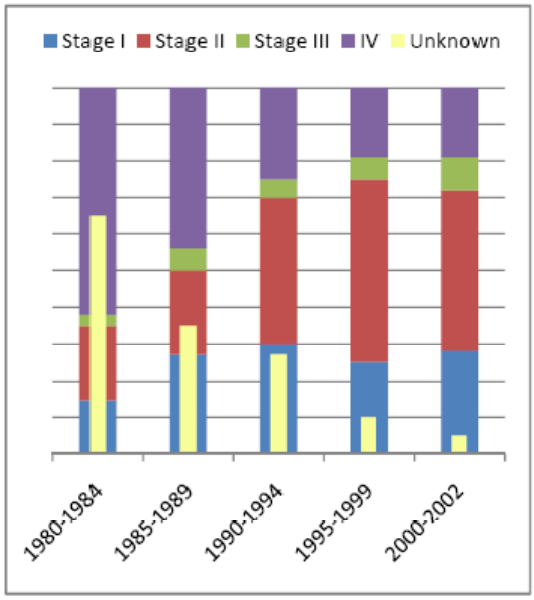


Figure 5.5b Stage of prostate cancer in men >70 years (NKR/IKC, 2007).

The stage in which prostate cancer is found, has a great influence on the survival rate of the patient. When prostate cancer is found and rightfully diagnosed at an early stage, these men have a better prognosis. In the US SEER data no clear evidence could be found that indicated this influence. However Dutch NKR data demonstrates this correlation. Figure 5.6 gives the prostate cancer survival rate distributed to the stage of prostate cancer at the date of first diagnosing. The survival rate of stage I prostate cancer is 100% after 10 years, while the surviving rate of stage IV prostate cancer is nearly 20% after 10 years. This difference is due to several facts, which includes the aggressiveness of the prostate cancer (type IV is more aggressive than type I) and the age of men when they are first diagnosed.

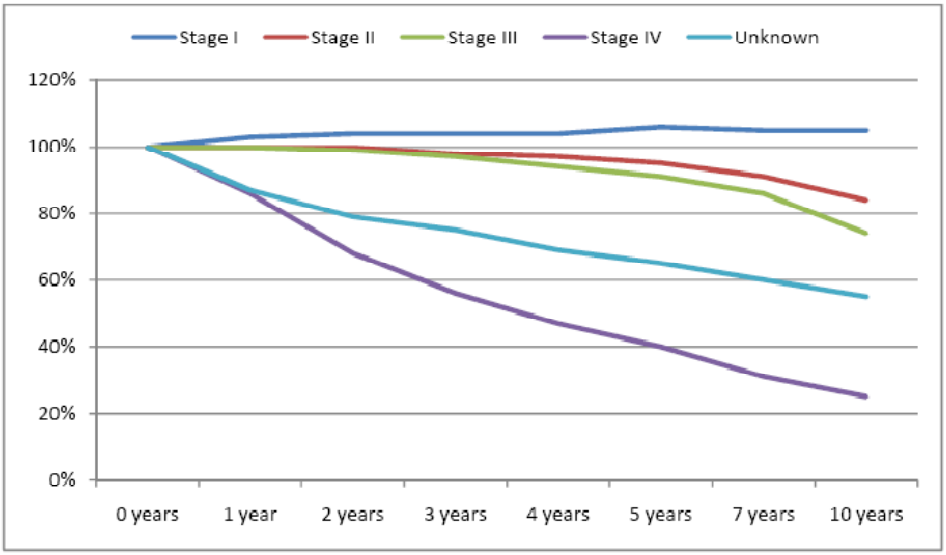


Figure 5.6 Prostate cancer survival rate distributed to stage of cancer (NKR/IKC, 2007).

5.1.3 Conclusion

In this paragraph, epidemiological trends concerning prostate cancer in the Netherlands are described. In literature and data retrieved from the Dutch Cancer Registration (NKR), three main trends were found. First the incidence rate of prostate cancer can be divided into four periods 1989 1992, 1992 1994, 1994 2000 and 2000 2003. In the first period, the incidence rate stayed more or less the same, in the second period the incidence rate increased dramatically. In the following period the growth of incidence rate stagnated, while in the last period the number of men diagnosed with prostate cancer increased again. Compared to the United States of America, there are major differences noticeable. For instance, the period in which the incidence rate first started to increase (NL 1992 1994; US 1989-1992). The second trend is the shift in age of men diagnosed with prostate cancer. Men are being diagnosed at a younger age than a few years ago; the same shift was noticeable in the US data. The last trend is the stage of prostate cancer when it is first detected in men. For five different periods research was performed in the stage distribution of prostate cancer. Since 1980-1984 the detection of early stage (I and II) prostate cancer increased a lot, while the number of late stage (III and IV) prostate cancer declined. Concluding we could say, the main epidemiological trends concerning prostate cancer in the Netherlands do not differ from the American trends, apart from the time shift in incidence rate in the Netherlands.

5.2 Diagnostics and treatment of prostate cancer in the Netherlands

Health care in the Netherlands has developed over the last decades. In this chapter the Dutch practice concerning prostate cancer will be described using different angles. First the Dutch practice concerning prostate cancer in the period 1975 1992 will be described in this paragraph.

NL practice (1975-1992)

In the Netherlands, men with urinary problems, such as being unable to urinate, consult a physician. The same was the case in the period 1975-1994. Diagnosing and detecting prostate cancer happened in the same way as in the United States in the period 1975 1988. After performing a medical history (asking the patient questions about his health), a physician would perform a physical examination. If the physician would suspect a condition such as prostate cancer, he would perform a digital rectal exam (DRE). If this test showed irregularities or hardness of the prostate a small biopt was taken and looked at by a pathologist. The treatment of prostate cancer, in this period, was performed by a physician who could choose between two different treatment options, surgery or radiation therapy. Both these treatment options were the same as used in the United States of America.

In this period approximately 4500 men were diagnosed yearly with prostate cancer (NKR/IKC, 2007). As shown in the first paragraph of this chapter, approximately 36% of prostate cancer found in this period was categorized as stage I or stage II (early stage) prostate cancer, 64% was diagnosed with advanced stage cancer (stage III or IV) (NKR/IKC, 2007). Compared to the American stage distribution of the prostate cancer found, more late stage (III and IV) prostate cancer was found in the Netherlands in this period.

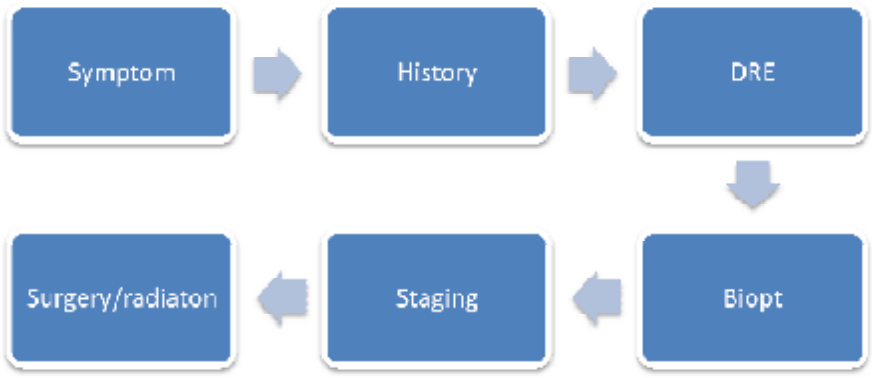


Figure 5.7 Practice of diagnostics and treatment of prostate cancer (1975-1992)

In the period prior to the introduction of PSA tests, the prognoses of men diagnosed with prostate cancer differed according as e.g. the stage of the prostate cancer. Men with early stage prostate cancer (stage I and II) had a higher chance of surviving the first five or ten years after the date of diagnosis than men with late stage prostate cancer (stage III and IV). However a lot of men died of prostate cancer in this period. Yearly approximately 2200 men died as a cause of prostate cancer (NKR/IKC, 2007).

5.3 Development and introduction of the PSA test in the Netherlands

5.3.1 Discovery of PSA

The discovery of prostate specific antigen took place in the United States of America in the period 1965-1986. However the knowledge about PSA found its way to the Netherlands. In 1992 the first PSA test was introduced and approved for monitoring purposes in the Netherlands, while in the US the first PSA test was approved in 1986. This means a delay of six years before the PSA test was introduced in the Netherlands, which raises the question of how this delay was possible? Cultural difference are thought to influence the adaptation of technological innovations (Jacobs & Theeuwes, 2005). Jacobs and Theeuwes conclude that the Netherlands has a somewhat withholding character. According to Hofstede (1984), this character can be explained by one of five factors that explain culture. That factors is the Masculinity or Femininity of a country. Hofstede explains: "*Masculinity stands for a preference in society for achievement, heroism, assertiveness, and material success. Its opposite, Femininity, stands for a preference for relationships, modesty, caring for the weak, and the quality of life*" (Hofstede, 1984). Masculine countries also have a preference for big and fast, while Feminine countries like small things and take it more slowly. The US are more Masculine than the Netherlands (62 versus 14), and therefore adopt new technologies more easily.

After the introduction of the PSA test in the United States of America, and prior to the introduction in the Netherlands, Dutch scientists and the Dutch government were reluctant in approving the use of the PSA test. First the PSA test had to meet Dutch criteria, and clinical trials were performed and guidelines were made (KWF Kankerbestrijding; GR, 2006; STOET & VKGN, 2005; NVU, 2007).

5.3.2 Introduction of PSA test in 1992

Afterwards, the PSA test was introduced to the Dutch health care sector in 1992. The purpose of the test was to follow patients after being diagnosed with and/or treated for prostate cancer (GR, 2006). The first PSA test

was therefore introduced to the Dutch health care sector as a monitoring tool, which could track the progress of the disease after treatment (Makarov & Carter, 2006), as was the case in the US in 1988.

Dutch medical professionals, who used the PSA test for monitoring purposes, also started using the test as a diagnostic tool. In 1994 the Food and Drug Administration (FDA) approved the first PSA test in the US used to detect prostate cancer in men 50 years and older, in combination with a DRE (FDA, 1994). This news reached the Netherlands, which contributed to the use of PSA test as a diagnostic tool in Dutch practices.

5.3.3 NL practice (1992 and further)

Except for the time difference, the Dutch practice of prostate cancer diagnosis does not differ from the American practice. Patients with health complaints went to consult a physician, who would conduct a series of test to determine the cause of the complaints. As well as the American, the Dutch medical specialist first were reserved with the approval of PSA tests being used to detect prostate cancer. They did acknowledge, however, the value of the PSA test as a monitoring tool. After the test being used successfully in the United States as a diagnostic tool, and after it being used more widely in the Netherlands, more physicians started to use the test as a diagnostic tool in combination with the already used DRE. In the early nineties, more prostate cancer patients were diagnosed, resulting in prostate cancer becoming the second most common cancer found in men (RIVM, 2007a).

In the United States of America researchers started to warn users of the PSA test, because it could not distinguish between prostate cancer and BPH. In the Netherlands research was also performed, to test the sensitivity of the PSA test (GR, 2006; GR, 2007b; KWF Kankerbestrijding). A new debate was born and especially the Dutch government expressed its concern for the public, and started signing up guidelines on how to use the PSA test.

One of these guidelines is drawn up by the Dutch Association of Urology, the Nederlandse Vereniging voor Urologie (2007). In this guideline all actions that need to be taken when prostate cancer is suspected, are outlined. For example the steps of diagnosing prostate cancer is first taking a history and performing physical examination, followed by a laboratory test. When these results are inconclusive or indicate prostate cancer, image building technologies and pathological research (biopt) must be used. The treatment plan and follow up care are also outlined in this report.

Apart from the concern about the PSA test itself, the government saw the costs for prostate cancer patients rise. The costs for the care of prostate cancer patients raised from 65 million Euros in 1999 to 92 million Euros in 2003. Of these 92 million Euros 52% went to hospital care and 36% to drugs and other aids. In the last decade the admission length has declined from eleven days in 1994 to seven days in 2004, but the day care

treatments have quadrupled in the same period. Due to the increasing detection of prostate cancer, the NKV expects the incidence to grow over the next few years. Because of the aging and the growth of the Dutch population, the NKV also believes the absolute number of men in which prostate cancer will be determined will grow with 56% in the period 2005-2025 (NKV, 2007). This means costs will rise even further in the future. Therefore the Dutch government has allowed researchers to examine whether screening for prostate cancer is an option to lower the costs.

5.4 Development and introduction of PSA screening in the Netherlands

As discussed in the previous chapter PSA screening uses the same technology as is used in monitoring and detecting prostate cancer; the PSA test. In this paragraph the social development of PSA screening in the Netherlands will therefore be described.

5.4.1 Development of PSA screening in the NL

PSA screening in the Netherlands is divided in three different types, individual screening, mass screening and screening in clinical trials. The first, individual screening, is performed in hereditary families only. In the Netherlands research is performed in the area of hereditary prostate cancer, which resulted in the knowledge that approximately 400 families in the Netherlands have hereditary prostate cancer (RIVM, 2007a). The second, mass screening for prostate cancer, is not performed in the Netherlands, since it is not allowed by the Dutch government. Some men, however, receive mass screening in the Netherlands. These men are part of clinical studies to examine the value of mass screening for prostate cancer, such as the European Randomized study for Screening for Prostate Cancers (ERSPC, 2008).

5.4.2 Introduction of PSA screening in the NL

Population screening is legally bound to the Wet op Bevolkingsonderzoek, WBO, in the Netherlands. This law prohibits persons to start mass screening for different purposes (Overheid.nl, 1992). Clinical trials have special permission to conduct population screening for scientific purposes. At this moment, the European Randomized study for Screening for Prostate Cancers is conducted in Rotterdam. In this trial, men in the age between 55 and 74 years get tested every four years for their PSA levels. The complete results for this trial are yet to be expected, despite this, a few conclusions can be drawn. From all men screened, 19% was found 'positive' in the sense that they have been further examined. From this group 20% was diagnosed with prostate cancer, which means 3,8% of the total screened population has prostate cancer (Schröder, et al., 1996; Roobol, Kirkels, & Schröder, 2003). We discussed the term of over-screening in the chapter about the American practice, but it also seems to be the case in the trial study held in Rotterdam. If we use absolute numbers, 100 men need to be

screened for 4 men to be diagnosed with prostate cancer, which means 96 men undergo unnecessary screening.

5.4.3 Public policy of PSA screening in the NL

The Dutch government can be considered a paternalistic government, which means it wants to protect its citizens from any form of harm. This also means that the government wants to control the health care sector, and its activities, such as population screening. As mentioned before, the right to conduct mass screening is bound by law. This law, the WBO, states that screening must reach at least the following five criteria (Overheid.nl, 1992);

- The test used must have a high specificity and sensitivity
- The disease must have an asymptomatic first stadium
- The disease must give better prognoses when treated in an early stage
- The test may not cause any harm or disadvantages
- The test has to be cost effective

Since the PSA test does not distinguish between prostate cancer and benign prostatic hyperplasia, the PSA test has a low sensitivity. Therefore, the first criteria is not met. The second and third criteria's are met by the PSA test, as prostate cancer does not show symptoms in the first stage. Practice also has shown prostate cancer is treated with better prognoses at an early stage. However, the PSA test causes harm to the public. Since it has a low sensitivity, a lot of men are over diagnosed and over treated. The fifth criteria also is not met at this moment, as no research has produced unambiguous results about the benefits of population screening. Despite this the costs for diagnosing and treatment of diseases in the Netherlands are known. The costs for a biopt are approximately 90 Euros (CTG/NZa, 2008), this does not include drugs and follow up care, and the costs for a PSA test, as it is performed by the Dutch general practitioners and other physicians, is 9 Euros (CTG/NZa, 2008).

Despite the fact that the PSA test does not meet the required criteria's, the Dutch Health Council, the Gezondheidsraad, has written an advice in which clinical trials conducted by the Erasmus Medical Center in Rotterdam, such as the ERSPC, are found in compliance with the WBO. This means that the Erasmus Medical Center has the privilege to conduct clinical trials concerning prostate cancer (GR, 2000; GR, 2007a). Clinical trials concerning screening for hereditary prostate cancer at the St. Radboud Medical Center in Nijmegen, are also found in compliance with the WBO (GR, 2001).

Clinical trials, such as the ERSPC, raise a lot of discussion with regard to whether or not to screen the public for prostate cancer. A lot of different actors participate in this discussion. The Dutch Society for General Practitioners, the Nederlandse Huisartsen Genootschap (NHG), for example, does not recommend individual

and mass screening for prostate cancer using the PSA test. In their guidelines concerning patients with urinary problems when prostate cancer is suspected, the NHG states screening for prostate carcinoma in patients without any symptoms is not advised. If a patient, after being consulted, does want to be screened, a general practitioner will perform a DRE and PSA test (NHG, 2004).

The Dutch Cancer Society, the KWF Kankerbestrijding, endorses this advice for as long as there is no scientific evidence that testing for prostate cancer, using the PSA test, in asymptomatic men is useful. The KWF Kankerbestrijding does consult men via their website about the pros and cons of PSA screening, such as; *(+) the PSA test can detect prostate cancer before I will get any complaints, (+) if treatment at an early stage is successful I will not be confronted with consequences of late stage prostate cancer, (-) if the PSA test shows high level of PSA and I do not have prostate cancer I have worried for nothing, (-) there is a risk of detecting prostate cancer while otherwise I might not have even noticed it* (KWF Kankerbestrijding).

The foundation for hereditary tumors in the Netherlands, Stichting Opsporen Erfelijke Tumoren (STOET), and the association of clinical genetics in the Netherlands, Vereniging Klinische Genetica Nederland (VKGN), have drawn up a guideline on screening for hereditary prostate cancer. They advice periodical examination in men who have first degree family members diagnosed with prostate cancer (such as a brother, a father or a son). Starting from the age of 50 years they should get a PSA test done ones every two years (STOET & VKGN, 2005).

In the next few years the results of the European screening program, ERSPC, will be known and better decisions concerning population screening can be made. Until these results are made public, the government does not allow public screening for prostate cancer in the Netherlands.

5.4.4 Conclusion

In the Netherlands screening for prostate cancer using the PSA test is prohibited by law. The PSA test itself is questioned, due to the low sensitivity of the test. Clinical trials however are performed in the Netherlands, in a European context of the ERSCP. PSA test are performed only by physicians and general practitioners; the covering societies of these physicians do not recommend individual screening. Individual screening is not performed in the Netherlands, except for the 400 hereditary families. This is the main difference with the United States, where individual screening is performed on a daily basis.

5.5 Conclusion

In this chapter major developments concerning the detection of prostate cancer in the Dutch health care system were described. Using the multi level model a comparison with the United States of America is made and a conclusion can be drawn.

In the period of 1975 1992 the detection of prostate cancer was part of the Dutch regime of diagnosing. Physicians used DRE to find irregularities which would result in further examination. The incidence rate for prostate cancer was low and the mortality rate was quite high in this period. In the US research was performed to improve technologies, and the Netherlands also performed research on this subject.

Different studies were performed in the US at niche level, which resulted in the discovery of PSA and the development of the PSA test. The Dutch government was cautious for the public and issued its own research in the Dutch health care sector, prior to an introduction of the PSA test. Because there was a need for better and more patient friendly diagnostic methods than the DRE, the PSA test was approved in 1992.

American research showed, the PSA test was a promising substitute for DRE. However, as time went by, different specialist warned users for the low sensitivity and specificity of the PSA test. Researchers in the Netherlands came to the same conclusions and advised the use of PSA test in combination with the DRE. The PSA test was slowly adopted in the existing regime of 1975 1992.

In the period of 1992 1994 more men were diagnosed with prostate cancer, and more functions of the PSA tests became known. The PSA test was started being used as a diagnostic more and more, while it had been introduced as a monitoring tool. For a small group of patients the test was also used as a screening tool. Research was performed on hereditary prostate cancer. A different regime for screening for hereditary diseases adopted the PSA test as a screening method.

In the same period the PSA test was also introduced as a screening test for all prostate cancer patients. The existing landscape of rules concerning population screening prohibited the use of PSA tests as a screening method for mass screening. It did however approve the use of PSA screening in clinical trials. Because this is screening at niche level, PSA screening has not yet reached the stage to where it can be adopted in a regime.

Comparison with the US

Compared to the United States of America, the development and introduction of the PSA test as a monitoring and diagnostic tool can be seen as similar, except for the time shift in the Netherlands.

The development and introduction of PSA screening on the other hand, can be considered different. Mass or public PSA screening is not adopted in both countries. In the United States national screening is not advised

yet, due to a lack of scientific results, and in the Netherlands mass screening for prostate cancer is prohibited by law. At niche level PSA mass screening is performed to examine its possibilities.

Despite the fact mass screening is not advised in the US, individual PSA screening is adopted in a regime of annual physicals and yearly screening for diseases. While individual PSA screening in the Netherlands is only performed for a very small part of the population in a regime for screening for hereditary diseases, it can be considered that individual PSA screening as it is performed in the US is not common in the Netherlands.

6. Development and introduction of PSA self test in the United States of America and the Netherlands

In this research the focus lies on the introduction and development of PSA tests and screening in the Netherlands. As mentioned previously in this report, at this moment in time more tests become available that can be performed at the level of the patient. These so called point of care tests are also upcoming in the field of prostate cancer through the introduction of PSA self tests. The developments concerning PSA self tests are therefore discussed in the context of broader developments towards more (possibilities for and promises of) point of care tests.

In this chapter first the developments in the practice of PSA tests are discussed, followed by a comparison between the developments in the United States of America and the developments in the Netherlands. The (future) developments in the practice of point of care tests are addressed in the last part of this chapter.

6.1 Development in the practice of oncology

The rapidly increasing patient population in the practice of oncology especially benefits from point of care testing, e.g. it can lead to a better quality of life and to a more effective resource utilization (Price, St. John, & Hicks, 2004). Every one in three people in the world will be affected by cancer at some stage in their life, as there are more than 200 types of cancer recorded, of which breast cancer (16%), lung cancer (13%), colorectal cancer (13%) and prostate cancer (12%) are the most common. Together these four cancer types account for more than half of all new cases in 2004 in Europe and in the United States of America (Cancer Research UK, 2007). Cancer is becoming a much more long term, chronic illness, due to improving survival rates. Technological and medical innovations have contributed to this development for the most part.

6.1.1 Contribution of POCT diagnostics in the practice of oncology

In the recent past, many innovations have contributed to the diagnostic, and treatment of cancers. Two major examples are in the field of radiology; the tomography imaging, which led to a pinpoint accuracy of localizing tumors, and in the field of laboratory medicine; genetic biomarkers that can aid in the field of screening, diagnosing & staging, management and prognosis of cancers (Price, St. John, & Hicks, 2004).

POCT in the diagnostic practice of oncology ensures faster and more informed clinical decisions. Where in the past, for example, a breast was removed when breast cancer was suspected, point of care tests now can avoid a radical breast removal and breast saving surgery becomes an option. This improvement leads to e.g. greater patient, and physician, satisfaction, as well as to reduced length of hospital stay due to less invasive therapies. POCT also reduces the number of patients being referred to hospital care for further examination, which in turn reduces overall health care costs (Price, St. John, & Hicks, 2004).

6.1.2 Contribution of POCT screening in the practice of oncology

Point of care tests are mainly used as first line tests to rule out the need for further examination, this can be considered as a screening method. According to Price, St. John and Hicks (2004), POCT is relatively cheap compared to other examinations such as biopsy. As well as the reduced costs, the possibility to allow the testing process to take place nearer to the patients also is a great contribution of POCT in the field of oncology. Price, St. John and Hicks believe the role for laboratory medicine as we know it, is the responsibility to ensure that a test can meet its expected requirements. Both in the United States of America (FDA) as in Europe (EMEA) medical instruments are only approved if they meet e.g. safety and quality standards.

6.1.3 Contribution of POCT in the practice of prostate cancer

In the Netherlands, a single prostate cancer risk management program, based on informed patients choice is used. While in the US, where medical decision making takes place in a more decentralized manner, an engaged public and commercial lobbying have led to a variety of opinions. As described in chapter four of this report, there are advocates of PSA testing saying that PSA tests have contributed in the decrease of prostate cancer mortality. There are also opponents who are concerned about the unnecessary detection and treatment in some cases. In the Netherlands the same debate is starting to rise, although it is discussed in a lesser degree.

6.2 US versus NL: similarities and differences in developments

First an overview of the developments concerning PSA self tests in the United States of America and in the Netherlands are discussed. At the end of this paragraph the similarities and differences are explained in the light of the multi level model described in chapter 2.

6.2.1 PSA self test in the United States of America

The PSA self test was introduced in the United States of America in the nineties. Despite the number of societal and laboratory issues in PSA screening, such as the specificity and sensitivity of the test, it was received enthusiastically. A large public interest and demand presumably led to this enthusiastic embrace of the new technology according to Price, St. John and Hicks (2004). In order to see if, at this moment in time, there (still) is a large public interest and demand towards PSA self testing, we conducted a small questionnaire.

Questionnaire

After talking to Stan Rosenfeld, a prostate cancer survivor and UCSF Medical Center Prostate Cancer Advocate in Marin County, CA, USA, an e-mail was send out to all 450 recipients. Due to a lack of time, there was only one week for the men to respond, and place of residence, we could only interview 15 men.

None of the men interviewed had ever heard of a PSA test that can be bought and performed by themselves. Two men did know about the possibility to go to a laboratory and ask for a PSA test to be performed. Most men (n=14) are interested or very interested in the possibility of PSA self testing. However they do have some reservations about several aspects of the test. Reactions to the PSA self test which were given the most by the interviewees, were reactions concerning the costs of testing, the time saved by not having to go to a laboratory, the convenience of performing the test at home (due to shame issues), and concerning about the interpretation of the test. (Survivors, 2007)

Although none of the interviewees had ever heard of the PSA self test, they are interested in the possibility of self testing. The statement of Price, St. John and Hicks (2004) that there was a large public interest and demand cannot be invalidated using this small questionnaire. However it does provide another side of the story, namely that not all men were aware of the possibility to test themselves for prostate cancer.

Laboratory PSA test versus PSA self test

Oberpenning et al. (2003) examined the agreement between laboratory based tests and the PSA self test that was introduced in 2001 in Germany, and found that this agreement lies just above random chance (53%). The sensitivity of the PSA self test was found to be 50% and the specificity 76%, opposite to a sensitivity and

specificity of respectively 44% and 94% in laboratory based tests. In the same study PSA self test performance and use was examined. These researchers also reported difficulties with test handling (24% had difficulties to produce sufficient amounts of blood), difficulties with interpreting test results (the test give ambiguous results for PSA concentrations close to the cutoff), psychological distress (due to false positive results) and the risk of missed diagnoses (caused by false negative results). A wider distribution and commercialization of the PSA self test is not recommended by these researchers, as the performance of the test is "*unsatisfactory and hardly superior to tossing a coin*" (Oberpenning, et al., 2003).

6.2.2 PSA self test in the Netherlands

Via the internet, commercial PSA self tests are available in the Netherlands. The test is, according to the distributors website, especially useful for men between 45 and 60 years. According to data consulted during this research, prostate cancer is most common in men older than 60 years. The distributor also claims the test sold is just as good as every laboratory PSA test available (MiraTes, 2008), while Oberpenning et al. (2003) found different results in their study. When the test results are positive, the instructions included in the test package, advice the man to consult a doctor (MiraTes, 2008). In 2000 the former Minister of Health in the Netherlands, announced that commercial sale of PSA self tests is distressing. In the same announcement she stated that rules and legislation must be drawn up to control the sale of these tests (Borst Eilers, 2000). The present Minister of Health in the Netherlands stated in an announcement that the sale of biomarkers, genetic tests, are only allowed by medical professionals and pharmaceutics. The sale of the PSA self test, and other tests, via the internet is therefore illegal. However, regulating the sale of these test via internet outside of the Netherlands is extremely difficult. The government and the Health Inspection of the Netherlands, the Inspectie voor de Gezondheidszorg (IGZ), are therefore focusing on the technical approval of the tests. MiraTes, one of the main distributors of self tests in the Netherlands, was selling uncertified instruments, and is therefore supervised by the IGZ. In 2009 the European guideline for diagnostic tests is evaluated, and Dutch guidelines will be adjusted accordingly (Klink, 2007).

The Dutch health council, the Gezondheidsraad (GR, 2007b), publishes a health report every year. In the 2007 report the discussion concerning the usefulness of self tests on human material was the central subject. The GR concluded that the developments towards more self tests, fits in the development in which the right of self determination of the human being is central. Self determination means that a patient decides on what happens with their body, and what does not. According to the GR (2007b), law and regulations in the Netherlands are

not yet applicable for regulating self tests. They state that the rules are ambiguous and can be interpret in several different ways. They also state that scientific evidence must be an important demand in evaluating self tests. They believe that four criteria; proved diagnostic value, proved effectiveness, favorable benefit risk ratio, and favorable cost-effectiveness ratio, must be publicized in scientific magazines. If that is not the case, the GR states that the quality of the test is not tested objectively. Another concern of the GR is the information services towards the consumer. They state that there is no sufficient information available for the consumer to make a well thought decision, which conflicts with the right of self determination (GR, 2007b).

Concerning the PSA self test, the 2007 report concludes that the diagnostic value or the PSA self test could not be determined. The CE assessments estimates the PSA self test in the moderate risk category, and the information given by the distributors of the PSA self test is insufficient and could cause harm to users. The GR also believes the supply of PSA self tests conflicts with Dutch laws and regulations as they are used at this moment in time. Because the effectiveness of early detection of prostate cancer is not scientifically proved, the benefit risk ratio and efficiency cannot be determined (GR, 2007b).

6.2.3 The United States of America versus the Netherlands

The main difference between the US and the Netherlands in the case of PSA self test, is the period after the introduction of the PSA self test. In the United States of America, the PSA self test was received enthusiastically, but is not used anymore at this moment in time. Due to the regime of individual screening in the US, the PSA self test is considered unnecessary. Men who want to get screened only have to consult a physician. In the Netherlands, where there is no regime of PSA screening, the necessity of a PSA self test is considered much higher. Dutch men only qualify for screening if they are considered high risk.

Therefore the reactions of both governments towards the test differ from each other. In the US the government is more worried about the clinical screening of patients, as that is the most common practice. While in the Netherlands the government focuses on the possibility of screening using the PSA self test.

6.3 (Future) possibilities of point of care technologies in the practice of prostate cancer

Now the development of PSA self tests and the differences between the United States of America and the Netherlands are more clear, first the (future) possibilities for POCT in the field of prostate cancer is discussed in this paragraph, followed by an example of a patients view on POCT.

6.3.1 (Future) possibilities for POCT in the practice of prostate cancer

The interpretation of point of care tests similar to the PSA self test, such as glucose or pregnancy tests, cause less reason for distress and are successfully embraced by users. So why is this not (yet) possible for the PSA self test? Although glucose meters use a meter reading and are therefore more difficult to use than the PSA self test, glucose meters are used on a regular basis. There are less difficulties performing a glucose test, because a diabetic patient gains experience in handling and interpreting tests results, as the test is used several times a week. In pregnancy tests, a positive result is based on a much higher level of hormones than the normal level. This results in an unambiguous result and a clearer signal. For the PSA self test, both characteristics are not applicable. Therefore there is more hassle concerning the PSA self test than there is in some similar tests.

Another emerging point of care technology in the field of prostate cancer are genetic tests, also known as biomarkers. In the Netherlands, researchers recently developed a new genetic test, called the PCA3. The PCA3 is not developed as a test to replace the PSA tests, but should be considered an extra aid in the decision of whether or not to proceed biopsy. The PCA3 is *prostate cancer* specific, in contradiction to the *prostate* specific PSA. This makes it possible to distinguish between prostate cancer and benign prostatic hyperplasia (BPH). Recent studies also report the PCA3 level can distinguish between non relevant and life threatening prostate cancer.

At this moment the PCA3 test is performed as a trial in the clinic (a urine sample is taken after undergoing a DRE), the sample is sent to a laboratory and the results are known within a certain period of time. Due to technological developments, researchers believe that genetic tests in the near future will become point of care tests (PCA3.org, 2007). Despite the test not being available to the public yet, UK Human Genetics Commission states genetic tests should not be sold directly to patients. They say the role of regulatory and professional bodies is to ensure stricter controls, to discourage home testing and sampling, and to engage in consumer education (Price, St. John, & Hicks, 2004).

6.3.2 Contribution of POCT through the eyes of a patient

Next to the future possibilities of POCT, the future use of POCT is quite important. For POCT is a relative new concept, not many patients have come in contact with it. In the practice of Diabetes Mellitus however, POCT has been used by patients for several years. Therefore this practice was chosen for the patients view.

A 30 year old woman was diagnosed with diabetes at the age of thirteen. Because she was a very active person her live changed radically, as she had to control her glucose intake and monitor her glucose blood levels regularly. "*By the time I was 16 years old diabetes had become a definite bore. I was fed up with the pressure of responsibility*." After years of testing and trying to come in peace with the disease, she now is in control: "*I have gotten to know a large number of people with diabetes, and many share my experiences. However, we are*

all different, and I am convinced that we each have individual needs. I am also convinced that personal ownership of one's body is vital for everyone, whether you have diabetes or not. We all look for some tools to indicate that our health is what we would want it to be. In my case, blood glucose and HbA1c testing are just two of the important tools, especially when they can be done by me or my diabetes specialist, when I am present" (Spriggs).

6.4 (Future) impacts in the practice of point of care technologies

A major change in health care is underway, a change towards a greater focus on patient demands and to a different way in which health care is delivered. However, typical cycle times for these "*break through innovations"* (Ridder, 2006) are between 10 to 15 years, as will be the same for point of care tests (Price, St. John, & Hicks, 2004). In this paragraph the (future) developments in the field of POCT are therefore described.

6.4.1 Greater focus on patient demands

The patient is becoming a more demanding costumer of health care services, due to emancipation and technological innovations. Every detail about health and health care is accessible throughout the world; websites such as the NCBI.gov and NIH.gov in the United States of America, and AD.nl and Elsevier.nl in the Netherlands give insights into the health care sector. The use of internet also allows a greater access to health and health care related information, making the patient a more informed costumer of health care services (Price, St. John, & Hicks, 2004). Care givers have to anticipate on this development.

As well as becoming more informed, patients also are more demanding costumers of health care services due to population growth. Because the entire population is growing, and the age of the population is increasing, more emphasis is placed on health care services. Due to the growing need for health care, related to the population growth, and the scarcity of health care resources, these resources must be must be used effectively. Another reason for the effective use of health care resources is the rapidly growing health expenditures in most Western countries.

A third cause of the more demanding consumer of health care services is modern society. Health care givers anticipate on the modern society in which emphasis is placed on well being and good health instead of caring for the ill. Health care is slowly shifting from cure and care to prevent illnesses.

6.4.2 The way in which health care is delivered

The shift from cure and care to a more prevention orientated health care sector changes the way in which health care is delivered. According to Price, St. John and Hicks (2004) point of care can change health care delivered in e.g. primary care, hospital organizations and laboratory medicine.

Primary care

Primary care in the Netherlands is seen as the first point of entry in the health care system. In the United States of America emergency departments of hospitals were always seen as the main point of entry, however this is changing. The importance of primary care has been noticed by the American government as it is much cheaper than emergency departments (Price & St. John, 2006).

The use of point of care tests in primary care can be implemented for several different practices and reasons. POCT can, for instance, be used in chronic disease management. It can also be used for monitoring health at distance using tele health. Through telecommunication such as the internet or telephone, chronic ill patients can be monitored. Diagnoses also can be made through video imaging using telecommunication.

Hospital organization

The focus on a more patient centered approach in health care is discussed in paragraph 6.4.1. Focusing on the patient, changes the hospital organization. Several years ago, patient care was delivered according to the services a hospital (or other care giver) had to offer. Nowadays patients demand on receiving the necessary care where they want it, and when they want it. For example, if a treatment only is available in a certain hospital, patients demand on getting the treatment in their own home town. This is, however, still not always possible, but care givers try to meet patients demand.

Because of this growing demand, hospitals try to be more desirable for the patient. In the Netherlands some insurance agencies decide where patients must go to in order to receive medical care, but some insurance agencies in the Netherlands, and the entire health care in the United States of America, do not. In this system patients can choose where they go to for health care services. One can imagine the reputation of a hospital plays a vital role in this system (AD, 2007). Next to improving hospitals reputation, hospitals also try to improve the quality of care and to reduce the length of stay.

POCT can contribute in hospital organizations to achieve previous described goals. It can also contribute e.g. in emergency departments for triage, in intensive care units for monitoring blood gasses and other departments (Price, St. John, & Hicks, 2004).

Laboratory medicine

As well as different health care departments, laboratories also are part of the hospital organization. Sometimes, however, laboratory medicine is not localized in hospitals, but form an individual and centralized organization. In the United States of America laboratories handle tests for a large region. In the Netherlands centralized laboratories are also common, but for small regions such as for the cities Enschede, Hengelo and Oldenzaal combined. These laboratories are mainly automated; large instruments are operated by trained specialists and are used for the most common tests, such as the PSA test.

The use of centralized laboratories brings along some negative side effects. In figure 6.1 all steps involved with laboratory testing are presented. Each step carries a risk, which can be minimized by minimizing the steps needed, as do point of care tests. The following risks can be reduced by performing POCT instead of laboratory medicine:

- Taking specimen from the wrong patient
- Mislabeling the sample
- Losing the sample on its way to the laboratory
- Performing the wrong test
- Delay the time from request to decision and action

Point of care tests can therefore also contribute to laboratory medicine.

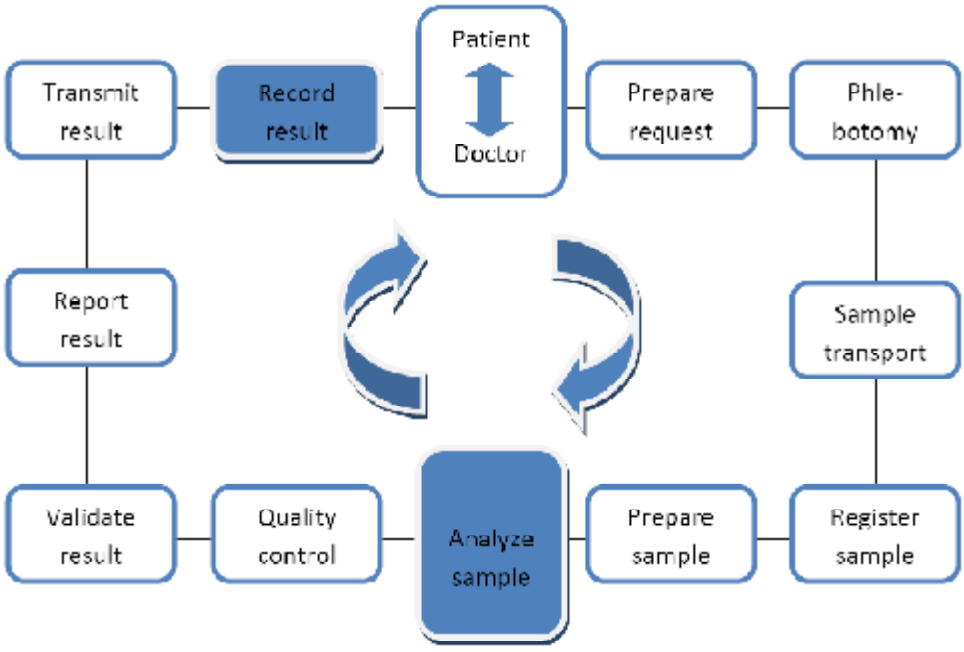


Figure 6.1 Steps involved making a test request using laboratory services. The blue boxes show the minimum number of steps for POCT (Price & St. John, 2006).

6.4.3 Conclusion

The (future) developments concerning point of care tests have been discussed in this paragraph. To summarize; point of care tests meet the necessary quality needs as it reduces medical errors, it meets the increased desires and needs of patients, and it alters patient doctor communication together with the increasing use of the internet and the increasing access to information.

Point of care tests are fit for use by non-laboratory personnel, and due to being small and less invasive for patients it is most likely POCT is used more and more in the future. Looking at health economics the costs of point of care tests are quite high, as is the case with most innovations at the stage of its first introduction. However, the value of 'normal' diagnostic tests are not being discussed, as no clinical trials are held between a group of patients treated for a disease with having a diagnostic test and a group without a diagnostic test.

According to Price, St. John and Hicks (2004), point of care tests are now reaching level of reliability and performance such that point of care testing devices can take their place alongside of other tools currently used by health care professionals. Guidelines and managerial tools, such as protocols, are now available to ensure that practice can be assured if followed properly. A number of studies illustrate the crucial role that point of care technologies can play in patient care and identify the benefits that can be increased from its application. The extent to which point of care technologies is used depends on the style of care and the way in which it is delivered.

6.5 Conclusion

Point of care technologies have contributed in several different ways to the practice of oncology. It has, for example, lead to more possibilities of diagnosing, screening, treating and monitoring different (chronic) illnesses. In a broader context POCT can lead to major changes in health care sectors throughout the world. The focus of the health care sector in the future will be on a greater patient demand and a different way in which health care is delivered.

At the level of primary care, in hospital organizations and in the field of laboratory medicine, as in much more other practices, point of care technologies will play a vital role in the future.

Developments at niche level are still being performed, such as the development of biomarkers and genetic test, which enables point of care technologies to seize more opportunities in the future.

7. Conclusion

In this chapter first the central research question is answered, followed by recommendations concerning the implementation of point of care technologies. Next to three different scenarios, a discussion of these results are also given in this chapter.

7.1 Conclusion

This research was performed to discuss the development and introduction of PSA tests and screening in the Netherlands. The prime question of this research is *What are the developments and expectations in the field of prostate specific antigen tests and what impacts of this prostate specific antigen test are likely to be expected on health care*, when looked at the United States of America and in the Netherlands.

7.1.1 The PSA case study versus the multilevel model

Using a multilevel perspective, major developments in the United States of America and the Netherlands were described in the previous chapters. The introduction of the PSA test in the diagnostic practice of the United States of America led to societal embedding of the technology. In the Netherlands this introduction also led to societal embedding, which means the PSA test is accepted and used in the way it was introduced. In the screening practice of the United States of America, the PSA test embedded in a new regime of annual physicals. This shift from an existing regime to another regime, whether or not this is a new or existing regime, can be considered a regime shift. PSA screening is not embedded in a regime in the Netherlands due to path dependency. Barriers at regime and landscape level were created for the PSA test as a screening method, such as rules and legislation. At landscape level PSA self test is discussed in terms of rules and guidelines in both countries.

7.1.2 What are the factors that influence the introduction of a technology learned from the PSA test?

The PSA test was chosen as the focus of this research, because it has undergone all transitions of the multilevel model. Since the PSA test can be described at all different levels of the model, conclusions can be drawn concerning point of care tests in general. The results of this research show the introduction of a technology, such as point of care tests, depends e.g. on [1] time, [2] organization and [3] culture.

[1] Due to the late introduction of the PSA test in the Netherlands, approximately four years later than in the United States of America, the technology was developed more. Also more knowledge concerning the innovation became known, which influenced the further introduction of the technology. [2] The way health care sectors are organized, differs from country to country, which also influences the introduction of point of care tests. In the case of PSA tests, for example, the technology could embed quite easily in the United States of America, due to the orientation on prevention in the health care sector. In the Netherlands, where the emphasis lies on cure and care, it could not embed that easily as a screening test. [3] The culture of a country also plays a vital role in the success rate of an innovation. When a country is aggressive in adopting innovations, an innovation can be introduced quite easily, which though does not mean it will automatically succeed. Due to the somewhat withholding character of the Netherlands, the introduction of innovations, especially medical innovations, will take longer than in the United States of America, which, however, does not mean it will not be introduced.

7.1.3 What are the developments of point of care tests in the Netherlands?

Both in the Netherlands as in the United States of America, research is performed in the field of point of care technologies. Biomarkers and genetic tests are developed and tested, while existing technologies are improved every day. In the Netherlands the discussion concerning biomarkers and genetic tests will go on, until, and probably far after, they have been introduced to the market. At this moment in time these tests are only performed in experimental, niche alike, settings. The real impact of these tests can, thus, only be estimated through scenario studies, such as this research. These studies are, however, very important as they can discuss, and partly predict, future developments and reactions towards innovations. The market, as well as the developers and distributors, are enabled to anticipate on expected developments described in scenario studies.

7.1.4 What are the future expectations of point of care tests in the Netherlands?

Despite the somewhat withholding character, innovations are being adopted in the Netherlands. So this will also be the case for point of care tests. Possibilities of this new innovation are becoming clearer every day as research is performed, both inside and outside the Netherlands. Despite the character of the Netherlands, much innovative research is performed at Dutch universities, laboratories and medical institutions in. In the region of the University of Twente in Enschede MESA+ (Institute for Nanotechnology), CTIT (Centre for Telematics and Information Technology), IMPACT (Institute of Mechanics, Processes and Control Twente), IBR (Institute for Behavioral Research) and IGS (Institute for Governance Studies), are some examples of research institutes concerning point of care technologies (Achterhuis, 1997).

7.1.5 What is the expected impact of point of care tests on future developments in the Dutch (NL) health care sector?

As mentioned in the chapter 6, a major change in health care is underway. This change, towards a greater focus on patient demands and to a different way in which health care is delivered, has a typical cycle time of 10 to 15 years. Although this change does not happen overnight, some changes already are visible. An example is the shift from cure and care towards a more preventive orientated health care sector. Another change that has been noticeable for several years now, the emancipation of patients, is expected to progress even further in the next couple of years. Next to this, increasing welfare has an impact on the image and perception of well being. While the welfare is increasing, due to e.g. technological innovations and growing knowledge, this perception also is expected to increase. Which, at the end, will place an emphasis on preventive health care instead of cure. In the near future, the way health care is organized also is expected to change. Health care services, which are nowadays delivered at hospitals, will move towards more specialized clinics near the patient, or even at point of care.

7.2 Recommendations

Based on this research some factors have become clear, concerning the development and introduction of PSA tests and other point of care tests in the Netherlands. Some recommendations are made in order to improve the introduction of these tests in the Netherlands. Because these recommendations can influence each other they are stated at random.

[1] The Dutch government can be considered as a somewhat withholding institution. This results in a slow adaption of innovations. In the Netherlands, first everything has to be discussed and considered prior to an eventual introduction (the Dutch call this the 'Poldermodel'). As Jacobs and Theeuwes (2005) described the Dutch government should invest in innovation; it should stimulate both economy and market in which the technology is introduced. This way new technologies can embed more quickly in the Dutch society and health care system.

[2] Introducing innovations, such as point of care tests, brings along a lot of discussion. The Netherlands should take into account, discussions held in other countries when discussing a new technology. A lot of time could be saved, as other countries, such as the United States of America, debate a lot of the same discussions. This phenomenon is also called benchmarking. As mentioned in the first recommendation, the Netherlands has a habit of discussing everything. This second recommendation does not mean, however, the Dutch government should discuss these discussion points all over again, as that will cost more time than it will safe. The wheel does not need to be re invented every time.

[3] The Dutch health care sector is slowly shifting from cure and care towards a more preventive orientated health care. This could benefit the Dutch government, as well as Dutch labor markets. Preventive medicine can predict if or when a person gets ill; It can prevent persons from getting ill; and it can prevent illnesses from worsening. All this saves a lot of money, e.g. in terms of less use of health care services. Less people get ill, or die from an illness, which is favorable for the labor market. There just are more people able to work. Especially with a negative population growth, which the Netherlands is facing, this last argument is a good reason to speed up the shift towards a more preventive orientated health care. Using point of care technologies, this process can be made easier.

[4] The new possibilities of point of care tests brings along a lot of uncertainty for users. Despite the information leaflets that come with self tests, users still have a lot of questions. These questions and uncertainties could lead to (patient or society) anxiety. The Dutch government and health care sector should anticipate on this. Rules, guidelines and protocols on how to use these tests are important to protect users from harm. However, user guidance on how to handle tests results also is recommended.

7.3 Scenarios

Using information gathered in this research, three scenarios for the Dutch future health care concerning POCT can be outlined; [1] preventive health care, [2] technological innovation of point of care tests, and [3] governmental investment in innovation. In this paragraph these scenarios are merely mentioned and not fully elaborated, as that was not the focus of this research.

[1] When the focus of the Dutch health care sector is placed on preventive care, point of care tests can be adopted and accepted better in the health care system. In this 'new' health care system, regularly check ups are offered more frequently to a larger group of people. This can be conducted either by primary care physicians (thus in the regular Dutch health care system) or by commercial organizations. Without point of care technologies, this shift from care and cure towards preventive health care, is not possible. Technologies as we now know it, are able to conduct preventive care. However, if preventive care is offered on a large scale, these technologies are no longer sufficient.

[2] At this moment in time, some point of care tests are considered radical technologies. When technological innovations and knowledge concerning point of care tests improve, these tests might be considered less radical. Medical innovations that are considered radical (or that require radical changes), such as break through innovations, are not easily adopted in the Netherlands. If the Dutch government would be less withholding and more aggressive, as is the American government, innovations would be adopted more easily.

[3] In some countries, such as in the United States of America, governmental institutes invest in research and development organizations, and therefore in technological innovation. In the Netherlands less investments are made in research and development of innovations. At small scale, research is performed at e.g. Dutch universities. However, due to a lack of governmental investments, these institutes are forced to sell their research, instead of conducting it on large scale themselves. Because large American organizations buy these researches, the United States of America accounts for the results. If the Dutch government was to invest more in innovations, more research could be performed and more knowledge would become available. If this is the case, scenario 2 could happen.

7.4 Discussion

In this paragraph limitations of this research in the way it was conducted, are outlined. Due to the nature of point of care tests, it is a relatively new concept, not much information is available. Information that was available, mostly is produced by bias actors. Governments, producers and distributors of the technologies can be considered as biased, as they have personal benefits in the product. Since the reliability of this research depends mostly on the reliability of the resources, this must be taken into account. Concerning the PSA tests, however, a lot of information was available. This was partly because of the controversies surrounding both the technology (PSA test) as the ailment (prostate cancer).

Focusing on a specific subject, such as the PSA test, does not always mean it is useful for answering a broader research question. This is probably also the case in this research. As described in chapter 2, there are three different forms of point of care tests. The PSA test can be considered as a handheld device. The results of this research can thus be transformed to this category quite easily. For the other forms, the handheld devices with meter reading and the bench top devices, the target group of the technology is entirely different. Despite this difference, the results of the PSA study can be transformed to these forms of point of care tests, be it in a altered manner. Next to the different forms of point of care tests, these tests can also be performed in different practices at different levels of the health care sector. The PSA test first was introduced at the hospital level. After a while it was used at societal level in the form of (individual) screening in the United States of America. The possibility to use the PSA test at point of care, enables the technology to be used at all different health care levels. Because of these broad applications of the PSA test, all aspects of health care could be addressed using this case. Therefore these results can be used in a wider context.

As research is performed and innovations are improved every day, this research becomes outdated fairly quickly. During the process of this research a lot of new information and reports became available. Due to deadlines and workload, I have chosen not to included these new reports in this research. Therefore the results of this research are not entirely up to date.

References

Achterbergh, R., Lakeman, P., Stemerding, D., Moors, E., & Cornel, M. (2007). Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: A sociotechnical analysis. *Health Policy* .

Achterhuis, H. (1997). *Van stoommachine tot cyborg. Denken over techniek in de nieuwe wereld.* Amsterdam: Uitgeverij Ambo bv.

ACS. (2003). American Cancer Society guidelines for the early detection of cancer, 2003. *CA Cancer J Clin* , 27-43.

ACS. (2007). *Estimated new cancer cases and deaths for 2007*. Retrieved 2 14, 2008, from http://seer.cancer.gov/csr/1975_2004/results_single/sect_01_table.01.pdf

AD. (2007, 8 31). *AD Ziekenhuis top 100*. Retrieved 4 14, 2008, from http://www.ad.nl/ziekenhuistop100/

Albertsen, P. (2006). PSA testing public policy of private penchant? *American Medical Association* , 2371 2373.

American Cancer Society. (2005). *Prostate cancer. Treatment guidelings for patients.* USA: ACS.

Angelis, G. D., Rittenhouse, H., Mikolajczyk, S., Shamel, L., & Semjonow, A. (2007). Twenty years of PSA: From Prostate Antigen to Tumor Marker. *Reviews in Urology* , 113-122.

ANP. (2007, Maart 6). Kankerbestrijding waarschuwt voor 'zelftest'. *Spits* , p. 6.

Bangma, C. (2002). *Urologie.* Houten: Bohn Stafleu van Loghum.

Beckman Coulter. (2008). *Prostate Cancer*. Retrieved 2 12, 2008, from http://www.beckmancoulter.com/products/applications/diseasemgmt/prostate.asp

Borst-Eilers, E. (2000). Antwoorden van de minister van Volksgezondheid, Welzijn en Sport op kamervragen van Kant over een test voor prostaatkanker. Kamerstuk: 2990014220. Den Haag: Tweede Kamer.

Cancer Research UK. (2007, 3). *Statistics on the most commonly diagnosed types of cancer in the UK*. Retrieved 4 4, 2008, from http://info.cancerresearchuk.org/cancerstats/types/?a=5441

Carroll, P. (2007, July 12). Urologist. (E. M. Jeckmans, Interviewer)

CBS. (2006, 5 15). *CBS. Kanker bij mannen nu doodsoorzaak nr.1.* Retrieved 2 12, 2008, from CBS: http://www.cbs.nl/nl NL/menu/themas/gezondheid welzijn/publicaties/artikelen/archief/2006/2006 1953 wm.htm

CNN.com/health. (2008, 1 16). *CNN*. Retrieved 2 13, 2008, from CNN: http://edition.cnn.com/2008/HEALTH/conditions/01/16/prostate.cancer.genes.ap/index.html

CTG/NZa. (2008). *Tarieven gezondheidszorg.*

Dennis, L. K., & Resnick, M. I. (2000). Analysis of Recent Trends in Prostate Cancer Incidence and Mortality. *The Prostate* , 247–252.

Drake, e. a. (n.d.). Gray's Anatomy for Students. Elsevier.

ERSPC. (2008, 1 12). *European study for screening for prostate cancer.* Retrieved 3 29, 2008, from http://www.erspc.org/

Etos. (2007). *Thuistest: snel en betrouwbaar testen.* Retrieved April 2, 2007, from Website of Etos: http://www.etos.nl/gezondheid/index.jsp?trg=gezondheid/index.thuistests

F.W.Geels. (2002). Technological transitions as evolutionary reconfiguration processes: a multi level perspective and case study. *Research Policy* , 1257 1274.

FDA. (1994, 8 29). *FDA approves test for prostate cancer.* Retrieved 02 25, 2008, from http://www.fda.gov/bbs/topics/ANSWERS/ANS00598.html

FDA. (2006, April 4). *FDA/CBER Testing yourself for HIV-1*. Retrieved April 2, 2007, from Website of FDA: http://www.fda.gov/cber/infosheets/hiv home2.htm

Ferrini, R., Steven, M., & Woolf, H. (1998). American College of Preventive Medicine Practice Policy. Screening for prostate cancer in American men. *American Journal of Preventive Medicine* , 81 84.

Frankel, S., Smith, G., Donovan, J., & Neal, D. (2003). Screening for prostate cancer. . *The Lancet* , 1122-1128.

Geels, F. (1998). Technological transistions as ecolutionary reconfiguration processes: a multi-level perspective and a case study. *Research Policy* , 1257 1274.

Geels, F., & Schot, J. (2007). *Typology of sociotechnical transition pathways.* University of Technology: Eindhoven.

GR. (2006). *Jaarbericht bevolkingsonderzoek 2006.* Den Haag: Gezondheidsraad.

GR. (2007b). *Jaarbericht bevolkingsonderzoek 2007. Zelftest op lichaamsmateriaal.* Den Haag: Gezondheidsraad.

GR. (2000). *Wet op bevolkingsonderzoek: prostaatkanker-ERSPC Rotterdam.* Den Haag: GR.

GR. (2001). *Wet op het bevolkingsonderzoek: Erfelijke prostaatkanker.* Den Haag: GR.

GR. (2007a). *Wet op het bevolkingsonderzoek: prostaatkanker-ERSPC Rotterdam.* Den Haag: GR.

Grix, J. (2004). *The foundations of research.* China: Palgrave MacMillan.

Group, U. M. (2007, 07). (E. Jeckmans, Interviewer)

Haggerty, J., Tudiver, F., Brown, J., Herbert, C., Ciampi, A., & Guibert, R. (2005). Patients anxiety and expectations. How they influence family phisicians decisions to order cancer screening tests. *Canadian Family Physician* , 1659 1667.

Hankey, B. F., Feuer, E. J., Clegg, L. X., Hayes, R. B., Legler, J. M., Prorok, P. C., et al. (1999). Cancer Surveillance Series: Interpreting Trends in Prostate Cancer—Part I: Evidence of the Effects of Screening in Recent Prostate Cancer Incidence, Mortality, and Survival Rates. *Journal of the National Cancer Institute* , 1017-1024.

Hofstede, G. (1984). Cultural dimensions in management and planning. *Asia Pacific journal of management* , 81 99.

Home Access. (2007). Retrieved April 2, 2007, from Website of Home Access: http://www.homeaccess.com/02/01/

Hugosson, J., Aus, G., Becker, C., Carlsson, S., Erikson, H., Lilja, H., et al. (2000). Would prostate cancer detected by screening with prostate specific antigen develop into clinical cancer if left undiagnosed? A comparison of two population based studies in Sweden. *BJU International* , 1078 1084.

i STAT. (2003). Biosensor technology. Portable precision. Measures in minutes.

Jacobs, B., & Theeuwes, J. (2005). Innovation in the Netherlands: the market falters and the government fails. *De Economist* , 107 124.

Kaplan, R. (2000). Two pathways to prevention. *American Psychologist* , 382 396.

Klink, A. (2007). Antwoorden op kamervragen van Kant over internetverkoop van biomarkertests. Kamerstuk 2755730. Den Haag: Tweede Kamer.

KNCV. (2005). *Aidstestje halen bij de drogist?*

KWF Kankerbestrijding. (n.d.). Retrieved October 23, 2007, from http://www.kwfkankerbestrijding.nl/

KWF Kankerbestrijding. (2007). *Biomarkers en kankerbestrijding. Gebruik van biomarkers bij erfelijkheidsonderzoek, diagnostiek en behandeling.* Amsterdam: Thieme.

KWF Kankerbestrijding. (2006, September 18). *Commerciële zelftesten*. Retrieved April 3, 2007, from Website of KWF Kankerbestrijding: http://www.kwfkankerbestrijding.nl/content/pages/Commerci%eble_zelftesten.html

Lapré, R., Rutten, F., & Schut, E. (2001). *Algemene economie van de gezondheidszorg.* Maarssen: Elsevier Gezondheidszorg.

LHV. (2008, 4 14). *PreventieConsult nieuw impuls voor vroege opsporing ziekten*. Retrieved 4 15, 2008, from http://home-open2.lhv.nl/resources/AMGATE_10899_1_TICH_R8824463210467/

Lindeboom, G. (1993). *Inleiding tot de geschiedenis der geneeskudne.* Rotterdam: Erasmus Publishing.

Makarov, D., & Carter, H. (2006). The discovery of prostate specific antigen as a biomarker for the early detection of adenocarcinoma of the prostate. *Journal of Urology* , 2383 2385.

McGregor, M., Hanley, J., Boivin, J., & McLean, R. (1998). Screening for prostate cancer: estimating the magnitude of overdetection. *Canadian Medical Association* , 1368 1372.

Merkerk, R. v. (2005). *Ontwikkelingen van Lab on-a chip technologie.* Utrecht: NanoNed/Universiteit Utrecht.

Merkerk, R. v. (2007, Maart 26). Promotieonderzoek. (E. Jeckmans, Interviewer)

MiraTes. (2008). *Gezondheidstests voor thuisgebruik*. Retrieved 4 5, 2008, from http://www.mirates.nl/

MiraTes. (2006, April 21). *MiraTes Cholesterol Zelftest +.* Retrieved April 3, 2007, from Website of MiraTes: http://www.mirates.nl/?file=141

MiraTes. (2006, October 23). *MiraTes Prostaat (PSA) zelftest - informatie.* Retrieved April 3, 2007, from Website of MiraTes: http://www.mirates.nl/?file=142

MiraTes. (2007). *MiraTes Prostaat (PSA) zelftest*. Retrieved April 3, 2007, from Website of MiraTes: http://www.mirates.nl/product/psa_test?path=102

Mitchell, D., Agle, B., & Wood, D. (1997). Toward a theory of stakeholder identification and salience: defining the principle of who and what really counts. *Academy of Management Review, Vol. 22, No. 4* , 853 886.

MNT Network. (n.d.). *i-STAT blood analysis chip: A new approach to point-of-care diagnostics enabled by microfluidics and biosensors.* Retrieved April 2, 2007, from Website of MNT Network: http://mnt.globalwatchonline.com/epicentric_portal/binary/com.epicentric.contentmanagement.servlet.ContentDeliveryServlet/MNT/Knowledge%2520Centre/Resources/MNT%2520Case%2520Studies/iSTAT%2520BLOOD%2520ANALYSIS%2520CHIP%2520A%2520NEW%2520APPROACH%2520TO%

Moors, E., Rip, A., & Wiskerke, J. (2004). The dynamics of innovation: a multilevel co-evolutionary perspective. In J. Wiskerke, & J. v. Ploeg, *Seeds of transition. Essays on novelty production, niches and regimes in agriculture.* (pp. 31 56). Assen: Royal van Gorcum.

NCI. (2007, 8 21). *The prostate specific antigen (PSA) test*. Retrieved 2 25, 2008, from National Cancer Institute: http://www.cancer.gov/cancertopics/factsheet/Detection/PSA

NCI. (2005). *What you need to know about prostate cancer.* USA: NIH.

NHG. (2004). *NHG standaard bemoeilijkte mictie bij oudere mannen (samenvatting) M42.* Utrecht: NHG.

NKR/IKC. (2007). *Cijfers: incidentie, sterfte en prevalentie*. Retrieved 03 20, 2008, from http://www.ikcnet.nl/

NKV. (2007, 12 13). *Prostaatkanker*. Retrieved 03 19, 2008, from RIVM Nationaal Kompas Volksgezondheid: http://www.rivm.nl/vtv/object_document/o1327n17277.html

NVU. (2007). *Prostaat carcinoom. Landelijke richtlijn. Versie 1.0.*

Oberpenning, F., Hetzel, S., Weining, C., Brandt, B., Angelis, G. D., Heinecke, A., et al. (2003). Semi Quantitative Immunochromatographic Test for Prostate Specific Antigen in Whole Blood: Tossing the Coin to Predict Prostate Cancer? *European Urology* , 478-484.

Overheid.nl. (1992). *Wet op het bevolkingsonderzoek (geldend op: 29-03-2008)*. Retrieved 3 29, 2008, from http://wetten.overheid.nl/cgi bin/sessioned/browsercheck/continuation=16896-002/session=012604690253202/action=javascript result/javascript=yes

PCA3.org. (2007). *Helping you decide when biopsy is right*. Retrieved 4 5, 2008, from http://www.pca3.org/public/about-pca3nl

PCF. (2005). *Report to the nation on prostate cancer. A guide for men and their families.* Santa Monica, CA, USA: PCF.

Price, C., & St. John, A. (2006). *Point of care testing for managers and policymakers. From rapid testing to better outcomes.* Washington DC: AACC Press.

Price, C., St. John, A., & Hicks, J. (2004). *Point-of-Care testing.* Washington DC: AACC Press.

Prostaat.nl. (2008). *Meer over PSA*. Retrieved 2 12, 2008, from Prostaat.nl: http://www.prostaat.nl/content/psa/psa.asp

Ridder, W. d. (2006). *Omgaan met doorbraakinnovaties. Een nieuwe democratische revolutie op komst.* Den Haag: SMO.

Rip, A., & Kemp, R. (1998). Technological change. In S. Rayner, & E. Malone, *Human choice and climate change. An International Assessment. Vol. 2* (pp. 327 399). Washington DC: Batelle Press.

RIVM. (2007a, 12 13). *Prostaatkanker*. Retrieved 2 12, 2008, from RIVM: http://www.rivm.nl/vtv/object_class/kom_prostaatkanker.html

Roobol, M., Kirkels, W., & Schröder, F. (2003). Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). *Britisch Journal International* , 48 54.

Rosenfeld, S. (2007, July 15). Patient Advocate. (E. M. Jeckmans, Interviewer)

RVZ. (2008). *Signalement goed patiëntschap.* Den Haag: RVZ.

Sackett, D., Rosenberg, W., Gray, J., Haynes, R., & Richarson, W. (1996). Evidence based medicine: what it is and what it isn't. *BMJ* , 71 72.

Scholtens, B. (2007, March 6). KWF vindt zelftest naar kanker onbetrouwbaar. *de Volkskrant* .

Schröder, F., Damhuis, A., Kirkels, W., Koning, H. d., Kranse, R., Nijs, H., et al. (1996). European randomized study of screening for prostate cancer. The Rotterdam pilot study. *International Journal Cancer* , 145 151.

Schwartz, L., Woloshin, S., Fowler, F., & Welch, H. (2004). Enthusiasm for cancer screening in the United States. *Journal of the American Medical Association* , 71-77.

SEER. (2007). *Cancer of the prostate.* Retrieved 2 12, 2008, from SEER Stat Fact Sheet: http://www.seer.cancer.gov/statfacts/html/prost.html

Smit, W., & van Oost, E. (1999). *De wederzijdse beïnvloeding van technologie en maatschappij. Een Technology Assessment-benadering.* Bussum: Uitgeverij Coutinho b.v.

Smith, R., Cokkinides, V., & Eyre, H. (2004). American Cancer Society guidelines to early detection of cancer, 2004. *CA A Cancer Journal for Clinicians* , 41-52.

Smith, R., Eschenbach, A. v., Wender, R., Levin, B., Byers, T., Rothenberger, D., et al. (2001). American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers: ALSO: Update 2001- testing for early lung cancer detection. *CA A Cancer Journal for Clinicians* , 38 75.

Spriggs, H. (n.d.). POCT a patients perspective.

Staal, S., & Floris, A. (2007). MediMate develops and markets electrolyte analyzers for the point-of-care.

Stamey, T., Yang, N., Hay, A., McNeal, J., Freiha, F., & Redwine, E. (2006). Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. In D. Marakov, & H. Carter, *The discovery of prostate specific antigen as a biomarker for the early detection of adenocarcinoma of the prostate.* (pp. 2383 2385).

Stemerding, D., & Swierstra, T. (2006). How might scenariostudies help us think about the normative implications of genomics and predictive medicine? In A. D. Bouvet, P. Boitte, & G. Aiguier, *Questions éthiques en médicine prédictive* (pp. 81 88). Paris: John Libbey Eurotext.

STOET & VKGN. (2005). *Hereditair prostaat carcinoom. Landelijke richtlijnen. Versie 1.0.*

Tonkens, E. (2003). *Mondige burgers, getemde professionals. marktwerking, vraagsturing en professionaliteit in de publieke sector.* Meppel: NIZW.

Voss, J., & Schectman, J. (2001). Prostate cancer screening practice and beliefs. A longitudinal physician survey. *J. Gen. Intern. Med.* , 831 837.

Vrouwe, E. X., Luttge, R., Vermes, I., & Berg, A. v. (2007). Microchip capillary electrophoresis for point of-care analysis of lithium. *Clinical Chemistry* , 1 6.

Weinmann, S., Richert Boe, K., Glass, A., & Weiss, N. (2004). Prostate cancer screening and mortality: A case control study (United States). *Cancer Cases and Control* , 113 138.

Whittemore, A., Kolonel, L., & Wu, A. (1995b). Prostate cancer in relation to diet, physical activity and body size in black, whites and asians in the United States and Canada. *Journal of the National Cancer Institute* , 652-661.

Whittemore, A., Wu, A., & Kolonel, L. (1995a). Family history and prostate cancer risk black, white and asian men in the United States and Canada. *American Journal of Epidemiology* , 732 740.

Widdershoven, G., Weijden, T. v., Ronda, G., Norg, R., Portegijs, P., Buntinx, F., et al. (2007). *Diagnostische zelftests op lichaamsmateriaal. Aanbod, validiteit en gebruik door de consument.* Maastricht: Caphri - Universiteit Maastricht.

Glossary

DRE	Digital rectal exam. The doctor inserts a lubricated, gloved finger into the rectum and feels the prostate through the rectal wall. The prostate is checked for hard or lumpy areas.
Incidence	The extent or rate of occurrence, especially the number of new cases of a disease in a population over a period of time.
Landscape	The environment of institutions, infrastructure, economical, political, social, cultural, legal and demographical relationships.
Mortality	Death rate.
Multilevel model	A theory about technological innovations that contains phenomena at three different levels (1) a micro level of technological *niches*; (2) a meso level of socio technical *regimes*; (3) a macro level of socio technical *landscapes*.
Niche	Relative protected locations for research and experimentation in which actors explore and learn about new technologies and their use.
Over diagnosing	Diagnosing tumors that would otherwise remain clinically unrecognized until the individual died from other causes.

Over-screening	Screening men who are not at high risk of developing the disease.
Over-treatment	Invasive treatment of the tumors that would unlikely be harmful.
PAP	Prostatic acid phosphatase. An enzyme produced by the prostate. It may be found in increased amounts in men who have prostate cancer, BPH or prostatitis.
POCT	Point of care testing. A test that can be performed directly at a patient's or consumer's level, of which the results are known immediately and will be used to make a decision and to take appropriate action, which will lead to an improved health outcome.
Prevalence	The total number of cases of a disease in a given population at a specific time.
Prostate cancer	A cancer located in the prostate of the male reproductive system. Some of the risk factors are age, family history, race, certain prostate changes and diet. Screening for prostate cancer can be done via *digital rectal* exam and *PSA test.*
PSA	Prostate specific antigen. A high PSA level is commonly caused by *benign prostatic hyperplasia* (an abnormal growth of the prostate), *prostatitis* (inflammation of the prostate) or *prostate cancer*.
PSA test	A laboratory test that shows the level of PSA in a man's blood sample. For this test a patient has to go to a laboratory where they draw little tubes of blood for the test. The test results are normally known within three days.

PSA self test	A test that shows the level of PSA in a man's blood sample and which can be performed at home or another private environment. For this test only a little drop of blood is required and the test results are known within five minutes.

Regime	Rule sets that are formed by established technologies and grant it stability.

TRUS	Transrectal Ultrasound. Ultrasound of the prostate gland via the rectal.

Appendix

First exploration of the literature

This research requires knowledge about different subjects, for each subject data from literature and interviews are used.

[1] First general knowledge about point of care technologies is required. The book *Point-of-Care Testing* by C.P. Price et al. (2004) will form the basis for this subject. This book points out the 'evolution' of diagnostics, everything between the first ways of diagnosis to the future of point of care technologies is covered in this book. Price and St. John (2006) also wrote a book specifically for health care managers and policymakers, *Point-of Care testing for managers and policymakers, from rapid testing to better outcomes*. This book is about the organizational side of POC testing.

[2] The second subject is the shift from cure and care to prevention in health care, or more specific the shift from monitoring disease to monitoring health. For general information about this shift, the following articles are studied amongst others: R.M. Kaplan (2000) *Two pathways to prevention*, and Smith, R.A., Cokkinides, V. & Eyre, H.J. (2004). *American Cancer Society guidelines to early detection of cancer, 2004.*

[3] The third subject of knowledge is prostate cancer and the accompanying diagnostic methods. Medical doctors and articles are addressed to explore this subject. Some of the articles are; Frankel, S., Smith, G.D., Donovan, J. & Neal, D. (2003). *Screening for prostate cancer*, and Smith, R.A., et al. (2001). *American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers: ALSO: Update 2001- testing for early lung cancer detection*.

[4] The opinion of the (possible) users will be the fourth subject of interest. This will be investigated through a small questionnaire, printed media and articles.

At last theories are used that helps give structure to this research. The theorie used to map the stakeholders is R.K. Mitchell et al. (1997), *Toward a theory of stakeholder identification and salience: defining the principle of who and what really counts*. W.A. Smit & E.C.J. van Oost (1999) *De wederzijdse beinvloeding van technologie en maatschappij, een technology assessment benadering* also is addressed. The first is about which stakeholders are important, the latter is about social maps and the interaction between the different stakeholders.

The theoretical framework of this research is a sociotechnical analysis using a multi-level perspective (MLP) (Geels, 1998) and the co evolution theory of A. Rip and R. Kemp (1998). The articles that are used are the following; Geels, F.W. (1998) *Technological transitions as evolutionary reconfiguration processes: a multi-level*

perspective and a case study. Stemerding, D., & Swierstra, T. (2006). *How might scenario studies help us to think about the normative implications of genomics and predictive medicine?* Achterbergh, R., et al. (2007). *Implementation of preconceptional carrier screening for cystic fibrosis and maemoglobinopathies: a sociotechnical analysis.* Rip. A., & Kemp, R., (1998) *Technological Change.* Geels, F.W., & Schot, J. (2007). *Typology of sociotechnical transition pathways*.

First exploration of possible case studies

Self tests are not new, as it has been over 30 years ago the pregnancy test was first introduced in the Netherlands as a self test. The introduction of this test rose a lot of debate in the 1970's, which is nowadays barely thinkable. Were women able to perform such a test? And is it responsible to diagnose pregnancy without intervention of a medical professional? These questions have been answered by current practices, and approximately a million pregnancy tests are sold in the Netherlands nowadays (Diagned).

Technological developments enable more diagnostic tests to be performed by a broad public, while before these test could only be performed by laboratories. In the last view years a lot of these new tests have been introduced, leading to a lot of discussion. In this section an overview of some new, and innovative, technologies is given. From this overview one case is chosen to examine in detail in order to discuss future developments and implications of point of care tests in general in the Netherlands.

Case 1 (Mirates PSA/cancer test):

Prostate cancer is in the fourth place of most occurring cancers. One out of thirteen men develop prostate cancer before they turn 80 (KWF Kankerbestrijding, 2007, p. 82). Prostate Specific Antigen (PSA) normally only exists in blood in small amounts (less than 4 ng/mL). A high amount of PSA in the blood could identify prostate ailment, not only prostate cancer (MiraTes, 2006). The PSA self test from MiraTes is available for Dutch clients on the internet for € 19.95 (approximately $26.50) (MiraTes, 2007). This test measures increased PSA levels using a droplet of blood from the finger. The test is a single use only test, and must be stored at room temperature. The MiraTes is currently not sold via MiraTes Europe BV because the product does not (yet) have CE marking, therefore it is now sold via MiraTes Asia.

In the information leaflet that comes with the test, MiraTes tells about warnings prior to use. The PSA level in the blood can be increased after riding a bike, within 24 hours after ejaculation, by men between 60 to 70 years, etcetera. They also guarantee the quality of the test, provided that the test was used in the right way. The pictures included in the information leaflet are quite clear, as are the expected results of the test (MiraTes, 2007).

The KWF Kankerbestrijding does not recommend the use of PSA tests for men without complaints. They state research still has to confirm whether PSA tests are accurate when there are no complaints. They also claim different PSA test do not give the same, unambiguous results (KWF Kankerbestrijding, 2006; Scholtens, 2007). While there is a lot of commotion in the Netherlands (KWF Kankerbestrijding, 2006; Scholtens, 2007; ANP, 2007), PSA self test, like the one from MiraTes, are commercially available in US supermarkets (Merkerk, Promotieonderzoek, 2007).

Case 2 (Cholesterol test):

The cholesterol test gives an indication of the total amount of cholesterol in the blood. High cholesterol levels indicates a higher risk on cardiac and vascular diseases. With a drop of blood derived from a finger, the test will show results within twelve minutes (Etos, 2007). The test is a single use, disposable test which must be at room temperature prior to use (MiraTes, 2006). An information leaflet is shown from the MiraTes cholesterol self test plus. The cholesterol test is legally available at pharmacies and large supermarkets in the Netherlands.

University of Twente
Enschede - The Netherlands

MiraTes Prostaat (PSA) ZelfTest – Gebruiksaanwijzing

Inhoud van de verpakking
1 witte folieverpakking met
- 1 witte testcassette
- 1 plastic pipet
- 1 pleister
- 1 gebruiksaanwijzing
- 1 vingerprikker
- 1 flesje buffervloeistof
- 1 zakje vochtvanger

Overige benodigdheden
Klok, horloge of timer met secondewijzer

Stap 1: Openen van de verpakking

Wanneer de MiraTes Prostaat (PSA) ZelfTest in de koelkast is bewaard, laat deze dan eerst op kamertemperatuur komen (15-30°C). Open de folieverpakking en gebruik de test binnen 1 uur na opening. Plaats de testcassette horizontaal op een schone en vlakke ondergrond. Het zakje met silica gel (vochtvanger) hoeft niet gebruikt te worden en kan weggegooid worden.

Stap 2: Voorbereidingen voor vingerprik

Was uw handen met zeep en warm water. Spoel ze goed af en maak ze droog voordat u met de test begint. Ga zitten en wacht ongeveer 5 minuten. Wrijf ondertussen uw handen, zodat ze warm worden. Om de bloedsomloop te bevorderen kunt u uw arm gedurende 30 seconden naar beneden laten hangen.

Stap 3: Vingerprik

Let op! De vingerprikker kan slechts éénmaal worden gebruikt

Draai het witte beschermstaafje ten minste twee maal helemaal rond.

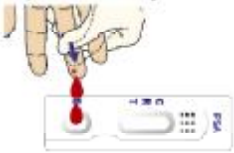
Trek vervolgens voorzichtig het witte beschermstaafje van de vingerprikker.

Plaats de vingerprikker op de zijkant van de top van uw vinger.

Zorg dat u de vingerprikker stevig op uw vinger gedrukt houdt terwijl u op de witte knop drukt.
Druk éénmaal stevig op de witte knop om de vingerprikker te activeren. Het naaldje trekt zich na activering direct terug. U zult een vrijwel pijnloos prikje in de vinger voelen.

Wrijf over uw vinger in de richting van de vingertop.

Stap 4: Bloed toevoegen



Houd uw vinger boven de sample well (S). Wrijf een aantal maal over uw vinger in de richting van de vingertop. Laat 2 hele druppels bloed direct vallen op de sample well (S).

Wanneer dit veel moeite kost, kunt u met behulp van de bijgeleverde pipet een hoeveelheid bloed op de sample well (S) aanbrengen die overeenkomt met 2 (vallende) druppels bloed.

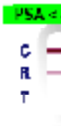
Stap 5: Buffer toevoegen

Draai het dopje van de buffer en voeg vervolgens 1 druppel buffer toe op de sample well (S). Start de timer of kijk op horloge of klok. Lees het resultaat af 5 minuten nadat u de buffer heeft toegevoegd.
Wanneer er na 30 seconden geen vloeistof in het uitslagvenster begint te lopen, voeg dan 1 of 2 extra druppels buffervloeistof toe.

Stap 6: Aflezen van het testresultaat

De testuitslag dient u precies tussen de 5 en 10 minuten na toevoeging van de buffervloeistof afgelezen te worden. Omdat na verloop van tijd de kleur kan veranderen, dient het resultaat niet later dan 10 minuten na toevoeging van de buffervloeistof afgelezen te worden. Tijdens het wachten kunt u de pleister op uw vinger plakken.

PSA < 4 ng/mL Normaal PSA-gehalte



Er verschijnt geen rode streep op de testlijn (T). Alléén de controlelijn (C) en referentielijn (R) verschijnen. Dit betekent, dat het PSA-gehalte lager is dan 4 ng/mL. U ris op basis van dit testresultaat geen reden tot nader onderzoek.

PSA 4 - 10 ng/mL Verhoogd PSA-gehalte

Wanneer de testlijn (T) lichter is dan de referentielijn (R), dan is het PSA-gehalte tussen 4 en 10 ng/mL. Hoe donkerder de testlijn (T), des te hoger het PSA-gehalte is. Voor mannen onder de 60 jaar is dit reden om een huisarts te raadplegen voor een bevestigingstest en eventueel vervolgonderzoek. Voor mannen boven de 60 jaar hoeft dit niet altijd zorgwekkend te zijn.

PSA < 10 ng/mL Verhoogd PSA-gehalte

Wanneer de testlijn (T) even donker is als de referentielijn (R), dan is het PSA-gehalte ongeveer 10 ng/mL. Voor mannen onder de 60 jaar is dit een reden om een huisarts te raadplegen voor een bevestigingstest en eventueel vervolgonderzoek. Voor mannen boven de 60 jaar hoeft dit niet altijd zorgwekkend te zijn, maar wel reden tot alertheid.

PSA > 10 ng/mL Verhoogd PSA-gehalte

Wanneer de testlijn (T) donkerder is dan de referentielijn (R), dan is het PSA-gehalte hoger dan 10 ng/mL. Een PSA-gehalte van meer dan 10 ng/L is altijd reden om contact op te nemen met de huisarts voor een bevestigingstest en eventueel vervolgonderzoek.

Ongeldig resultaat:

De controlelijn (C) en/of referentielijn (R) verschijnen niet. Onvoldoende bloed of een incorrecte uitvoering zijn de meest voorkomende oorzaken van een ongeldig testresultaat. Wanneer dit uitgesloten kan worden, neem dan direct contact op met MiraTes. Gooi de test niet weg.

Advies en verwijzing

Wanneer de MiraTes Prostaat (PSA) ZelfTest een verhoogde PSA-waarde aangeeft (hoger dan 4 ng/mL), moet dit niet als absoluut bewijs van een verhoogd PSA of prostaataandoening geïnterpreteerd worden. Uitslagen die wijzen op een verhoogd PSA-gehalte dienen altijd te worden bevestigd door andere testmethoden. Wij raden aan om in dit geval contact op te nemen met uw huisarts.

Afval

Wanneer u de MiraTes Prostaat (PSA) ZelfTest succesvol heeft uitgevoerd, stop dan alle onderdelen terug in het originele doosje en deponeer het bij het huishoudelijk afval.

Service

MiraTes besteedt veel zorg aan zijn producten. Om hoogwaardige services en producten te kunnen blijven leveren, verneemt wij graag uw opmerkingen of suggesties. U kunt uw vraag of opmerking naar ons sturen via het service formulier op onze website www.mirates.nl. Wij zullen u dan zo spoedig mogelijk van een antwoord voorzien. Mocht u vragen hebben over de uitvoering van de test of de betekenis van het testresultaat, dan zult u de meeste antwoorden vinden bij "de meest gestelde vragen" op www.mirates.nl.

☎ 00 800 46 63 83 78 (vast netwerk gratis)

MiraTes Asia Ltd
c/o MiraTes Europe BV
Calandstraat 60
3047 AC Rotterdam
Nederland

T +31 (0) 10-262 13 38
F +31 (0) 10-262 43 71
E service@mirates.com
I www.mirates.nl

University of Twente
Enschede - The Netherlands

MiraTes Cholesterol ZelfTest + - Gebruiksaanwijzing

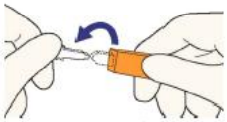
Inhoud van de verpakking
- 1 witte folieverpakking met een witte totaalcholesterol testcassette
- 1 witte folieverpakking met een witte HDL-cholesterol testcassette
- 1 gele conversietabel totaalcholesterol
- 1 oranje conversietabel HDL-cholesterol
- 3 oranje vingerprikkers
- 2 pleisters
- 1 gebruiksaanwijzing

Overige benodigdheden
Klok, horloge of timer met secondewijzer.

Stap 1: Voordat u begint
Lees voor gebruik eerst of de test geschikt voor u is.
Wanneer de MiraTes Cholesterol ZelfTest + in de koelkast is bewaard, laat deze dan eerst op kampertemperatuur komen (15-30°C). Open vervolgens één van beide folieverpakkingen en gebruik deze test zo snel mogelijk. Open de folieverpakking van de tweede test niet voordat u klaar bent om ook deze uit te voeren. Het maakt geen verschil met welke test u begint. Beide testcassettes worden op dezelfde manier uitgevoerd. **Let op!** Gebruik voor iedere testcassette een andere vinger. Het zakje met silica gel (vochtvanger) hoeft niet gebruikt te worden en kan weggegooid worden.

Stap 2: Voorbereidingen voor vingerprik
Was uw handen met zeep en warm water. Spoel ze goed af en maak ze droog voordat u met de test begint. Ga zitten en wacht ongeveer 5 minuten. Wrijf ondertussen uw handen, zodat ze warm worden. Om de bloedtoevoer te bevorderen kunt u uw arm gedurende 30 seconden naar beneden laten hangen.

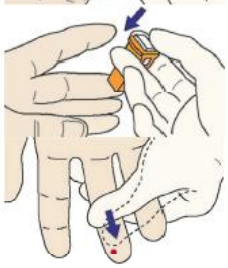
Stap 3: Vingerprik
Let op! De vingerprikkers kunnen slechts éénmaal worden gebruikt.



Draai het witte beschermstaafje ten minste twee maal helemaal rond.

Trek vervolgens voorzichtig het witte beschermstaafje van de vingerprikker.

Plaats de vingerprikker op de zijkant van de top van uw vinger.



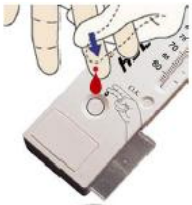
Zorg dat u de vingerprikker stevig op uw vinger gedrukt houdt terwijl u op de witte knop drukt.

Druk éénmaal stevig op de witte knop om de vingerprikker te activeren. Het naaldje trekt zich na activeren direct terug. U zult een vrijwel pijnloos prikje in de vinger voelen.

Wrijf over uw vinger in de richting van de vingertop.

Let op! Gebruik voor iedere testcassette een andere vinger.

Stap 4: Bloed toevoegen



Het bloed dient binnen 5 minuten toegevoegd te worden.

Houd uw vinger boven de zwarte cirkel. Wrijf een aantal maal licht over uw vinger in de richting van de vingertop, zodat er een druppel bloed verschijnt. **Let op!** Te hard drukken kan het testresultaat beïnvloeden.

Laat de druppel bloed los op de bodem van de test in het midden van de zwarte cirkel. Ga hiermee door tot de zwarte cirkel niet meer zichtbaar is. Als de zwarte cirkel nog zichtbaar is, dient u door te gaan met het toevoegen van bloed.

Zodra de zwarte cirkel niet meer zichtbaar is, tikt u de testcassette met de onderkant (waar de doorzichtige flap zit) op het tafeloppervlak en leg de test vervolgens plat op tafel. Nu dient u nog 3 tot 4 minuten te wachten voor u verder gaat met stap 5.

te weinig bloed | te weinig bloed | genoeg bloed

Stap 5: Test activeren

Pak de test stevig in uw hand. Trek vervolgens stevig aan de doorzichtige flap, die zich aan de rechterzijde van de test bevindt, totdat u de volledige pijl kunt zien. Trek hard. Wees niet bang de flap kapot te trekken of bloed te morsen.

De OK-indicator zal na een paar minuten paars worden. Vervolgens zal er een blauwpaarse lijn verschijnen in het venster naast de schaalverdeling. De END-indicator wordt groen na ongeveer 12 minuten.
Lees het testresultaat af nadat de OK- én de END-indicatoren zijn verkleurd.

Stap 6: Aflezen van het testresultaat
Lees het resultaat af bij helder licht. Zoek het uiterste puntje van de blauwpaarse lijn, ook al is deze onduidelijk of vaag. Lees vervolgens de bijbehorende waarde op de schaalverdeling af. Dit getal is het testresultaat en niet uw cholesterolgehalte.

Met behulp van de gele en oranje conversietabel kunt u het cholesterolgehalte (in mmol/L) aflezen, die bij de betreffende waarde hoort. Noteer deze waarde.

Let op! Gebruik de conversietabel die overeenkomt met de testcassette om het cholesterolgehalte te bepalen. Gebruik alléén de bijgeleverde conversietabellen. Tabellen van andere tests kunnen onjuiste uitslagen geven.

Afval
Alle onderdelen van de MiraTes Cholesterol ZelfTest + vallen onder de categorie restafval en kunnen gewoon bij het huishoudelijk afval.

Interpreteren van uw risico op hart- en vaatziekten
Wanneer u beide testcassettes heeft uitgevoerd en de bijbehorende resultaten heeft genoteerd, deel dan de waarde van het totaalcholesterol-gehalte (in mmol/L) door de waarde van het HDL-cholesterol (in mmol/L):

$$\frac{\text{Totaalcholesterol-gehalte}}{\text{HDL-cholesterolgehalte}}$$

Voorbeeld:
De waarde van het totaalcholesterol-gehalte is 5,4 mmol/L.
De waarde van het HDL-cholesterol is 1,8 mmol/L.
De totaalcholesterol/HDL-ratio is dan (5,4 : 1,8 =) 3
Uit de onderstaande tabel blijkt vervolgens, dat het risico op hart- en vaatziekten niet verhoogd is.

Totaalcholesterol/HDL-ratio

	Man (♂)	Vrouw (♀)
Geen verhoogd risico	< 5,0	< 4,5
Licht verhoogd risico	5,0 – 6,5	4,5 – 5,9
Verhoogd risico	6,5 – 8,0	5,9 – 7,3
Sterk verhoogd risico	> 8,0	> 7,3

Service
MiraTes besteedt veel zorg aan zijn producten. Om hoogwaardige service en producten te kunnen blijven leveren, vernemen wij graag uw opmerkingen of suggesties. U kunt uw vraag of opmerking naar ons sturen via het service formulier op onze website www.mirates.nl. Wij zullen u dan zo spoedig mogelijk van een antwoord voorzien.

Mocht u vragen hebben over de uitvoering van de test of de betekenis van het test resultaat, dan zult u de meeste antwoorden vinden bij "*de meest gestelde vragen*" op www.mirates.nl. U kunt ook bellen met onze gratis medische helpdesk:

☎ **00 800 46 63 83 78 (vast netwerk gratis)**

MiraTes Europe BV
Cailrostraat 60
3047 BC Rotterdam
Nederland

T +31 (0) 10-262 13 38
F +31 (0) 10-262 43 71
E service@mirates.com
I www.mirates.nl

MIRATES

Bezoek ook eens onze internetsite voor informatie over onze producten:
www.mirates.nl

o

Case 3 (STD/HIV/Aids tests):

In 1996, the US Food and Drug Administration (FDA) approved the use of home HIV tests. The blood tests "The Home Access HIV 1 Test System" of "The Home Access Express HIV 1 Test System" are manufactured by Home Access Health Corporation (FDA, 2006). First you have to take blood from your finger and then send it to a laboratory. The results will be known within 3 to 7 days (Home Access, 2007). This test is not a POC blood test as the results are not ready at the level of the patient. The only HIV test that does not have to be sent to a laboratory uses mucous membrane form the mouth instead of blood (KNCV, 2005).

Case 4 (Bipolar disorder)3:

MediMate, a spin off from MESA+ and BMTI institutes of the University of Twente, uses electrophoresis for detecting lithium in blood. Lithium is the number one medication for manic depressive illness. Because of its toxicity at high levels this drug use must be monitored on regular basis. This technology is still at a research phase, more clearly at the clinical trial phase (Staal & Floris, 2007).

An electric field is used across a micro channel to separate and detect lithium in only several seconds. Chemical separation is performed on a standard glass microchip. Using this technology, sodium, lithium, magnesium and calcium can be measured. A study shows "the new microchip, with CE mark, provides a convenient and rapid method for point of care testing of electrolytes in serum and whole blood" (Vrouwe, Luttge, Vermes, & Berg, 2007).

Case 5 (i-STAT)4:

With the integration of biochemical and silicon chip technologies, i STAT combines a portable system with laboratory accuracy and precision results. The i-STAT uses single, disposable cartridges which combines calibration and testing of the sample in the same device.

The cartridges must be stored in a cool place (2 8°C or 35 46°F) and have to be at room temperature prior to use. The sample has to be a fresh blood sample deriving from artery, vein or skin puncture. The volume of the test sample has to be between 16 µL and 95 µL depending the cartridge (a normal drop of water measures approximately 50 µL). The test has to be performed within 30 minutes, again depending on the cartridge used.

[3] Note: this information comes from MediMate.

[4] Note: this information comes from i STAT Corporation.

The analysis of the blood sample takes between 130 (approx. 2 min.) and 1000 seconds (approx. 16 min.) depending on the test used (i STAT, 2003). For information about different analyses, see Appendix III.

The i-STAT has a built in quality at every step. The i STAT uses high quality materials which gives each cartridge a high level of accuracy and reliability before the measurement. During the measurement, built in quality control procedures watch the quality. From monitoring the quality of the sample to validating the reagent chemicals. When quality cannot be guaranteed, the results of the analysis will not be displayed. The i-STAT also provides reporting capabilities to monitor operator and machine performance regardless of the location of the testing. (i STAT, 2003)

i STAT was founded in 1983 and is now part of Abbott Laboratories (since January 2004). The i STAT blood analysis chip was first launched in the market in 1995, the underlying technology dates from the mid 1980s (MNT Network). In the Netherlands the UMC Utrecht uses the i STAT as is the MST in Enschede (Merkerk, Promotieonderzoek, 2007). In the US the i STAT has been used for a long time, in the Netherlands the i STAT is used since 2000 (Merkerk, Ontwikkelingen van Lab on a chip technologie., 2005).

University of Twente
Enschede - The Netherlands