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EVALUATING MELANOMA TREATMENT COSTS BASED ON ESTONIAN HEALTH INSURANCE FUND DATABASE – POSSIBILITIES FOR DECREASING COSTS WITH EARLY DETECTION SUPPORTED BY TELEDERMOSCOPY

Master's thesis

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MELANOOMI RAVIKULUTUSTE HINDAMINE HAIGEKASSA ANDMETE PÕHJAL – VÕIMALUSED KULUDE VÄHENDAMISEKS, SUURENDADES VARAJAST AVASTAMIST TELEDERMATOSKOOPIA ABIL

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

Background: Malignant melanoma is the deadliest form of skin cancer with high potential of spreading to other parts of the body. With increasing trends in patient numbers, there is a need to promote primary prevention and early detection. *Aim:* The aim of this thesis is to evaluate costs of melanoma diagnosis and treatment and investigate the possibility of decreasing costs by increasing early detection with using teledermoscopy in Estonia. *Methods:* A retrospective registry-based study from 2006 to 2016 was conducted including patients with malignant melanoma. Using medical bills from Estonian Health Insurance Fund, a cost-consequence analysis was carried out. *Results:* There were in total of 5830 melanoma patients – 4652 in early detection group and 1178 in late detection group. Melanoma diagnosis and treatment costs were found to differ 2-3 times between the subgroups. By increasing the proportion of early detection melanoma patients, it is possible to decrease the overall spendings. For promoting early detection, teledermoscopy could be used as a supportive tool as it has been found to offer better access to care and more precise diagnosing compared to conventional care. *Conclusions:* By increasing the use of teledermoscopy as a supportive tool for diagnosing, it can have a positive effect on early detection due to accessibility of dermatologist opinion and therefore, reduce the overall costs of melanoma treatment by lowering the burden of late stage treatment costs.

This thesis is written in English and is 60 pages long, including 6 chapters, 8 figures and 10 tables.

Annotatsioon

Melanoomi ravi kulutuste hindamine Eesti haigekassa andmete põhjal – võimalused kulude vähendamiseks, suurendades varjast avastamist teledermatoskoopia abil

Melanoom on kõige agressiivsem nahavähi vorm ning see võib kiirelt organismis edasi levida. Kiire haigestumise tõus elanikkonna seas nõuab aktiivset esmast ennetustegevust ning võimalikult varajast haiguse avastamist. *Töö eesmärk:* Magistritöö eesmärgiks on uurida kulutusi, mis on seotud melanoomi diagnoosimise ja raviga ning uurida kas neid kulutusi on võimalik vähendada kasutades teledermatoskoopiat varajaseks diagnoosimiseks. *Meetodid:* Teostati retrospektiivne registripõhine uuring ajavahemikus 2006 kuni 2016, kuhu kaasati kõik patsiendid, kellel oli diagnoositud melanoom. Kasutades Eesti haigekassa raviarveid, viidi läbi kulu-tulemuse analüüs. *Tulemused:* Kokku oli 5830 patsienti, kellest 4652 olid varajase avastamise grupis ning 1178 hilise avastamise grupis. Melanoomi diagnoosimise ja ravi kulused kahe grupi vahel erinesid 2-3 korda. Suurendades varajase avastamise osakaalu patsientide seas, on võimalik üldisi kulutusi vähendada. Varajase avastamise suurendamiseks võiks kasutada teledermatoskoopiat, kuna on leitud, et see suurendab arstiabi kättesaadavust ning võimaldab täpsemat diagnoosimist. *Kokkuvõte:* Suurendades teledermatoskoopia kasutust, on võimalik suurendada varajast avastamist ning seeläbi vähendada melanoomi ravi kulutusi.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 60 leheküljel, sisaldades 6 peatükki, 8 joonist, 10 tabelit.

List of abbreviations

CA	cost analysis
CBA	cost-benefit analysis
CCA	cost-consequence analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
EHIF	Estonian Health Insurance Fund
HTA	health technology assessment
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10^{th} revision)
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
SLNB	sentinel lymph node biopsy
WHO	World Health Organization

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1 Introduction

Telemedicine – as defined by WHO – is "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities" [1]. It is an expanding area offering an alternative to traditional in-person healthcare. Telemedicine is often seen as an attractive option as the aim of telemedicine is to increase the quality of care with optimised use of resources [2]. As dermatology is a very visual branch of medicine, it is perfect for such care model [3]. Teledermatology – either synchronous or asynchronous – is used to diagnose and treat patients by sharing visual images of skin lesions with the remote dermatologist. When the images are taken using epiluminescence microscope, the technology is called teledermoscopy [4].

Malignant melanoma is the most aggressive type of skin cancer being accountable for majority of skin cancer deaths. Melanomas can form anywhere on the skin as well as in the eyes, mouth, genitals, and anus [5]. What makes melanoma such a deadly cancer is its high probability of metastasis, even in early disease progression. The most common sites of regional metastasis are nearby skin, sub-cutaneous tissue, and lymph nodes. For distant metastasis, the most common sites are lungs, brain, liver, bones, and intestine [6]. Based on the US melanoma statistics, 84% of all new melanoma cases are localized, 9% regional, and 4% distant. Melanoma is curable when detected early – 5-year relative survival for localized melanoma is 98.4%, 63.6% for regional and 22.5% for distant melanoma [7]. The prevalence of melanoma has been increasing over the past years and the patient numbers are expected to grow in the future as well [8]. Therefore, it is important to contribute to prevention strategies and early detection.

The increase in reliability and accuracy of diagnostic and management decisions made using teledermoscopy is supported by multiple studies [9]–[11]. It has been shown that it is possible to notably reduce the secondary care visits and allow better access to care by

implementing teledermatology. The economical evaluations of using teledermatology have shown the cost-effectiveness of the intervention mostly form the societal perspective [12]. However, the impact on costs by using teledermoscopy as a supportive tool for early detection of melanoma treatment, has not been researched further. By being more accessible and supported, teledermoscopy could have a positive effect on early detection and therefore have a cost on total melanoma treatment due to decrease of late stage treatment cost.

In this thesis, the fields under research are economic evaluations and telemedicine. The economic evaluations are further narrowed down to cost-consequence analysis. As telemedicine affects both health outcomes and costs, a possibility to reduce costs was brought into investigation by teledermoscopy service. The aim of this thesis is to evaluate costs of melanoma diagnosis and treatment and investigate the possibility of decreasing costs by increasing early detection using teledermoscopy in Estonia.

The objectives of the research paper are:

- To distinguish patient profiles between early and late detection of melanoma;
- To assess the costs associated with diagnosis and treatment of melanoma;
- To assess the possible teledermoscopy impact to diagnosis and treatment costs by detecting the disease early.

The research seeks to answer the following questions:

1. What costs are associated with diagnosis and treatment of melanoma in Estonia?
2. How costs differ between different patient profiles?
3. What effect on costs has detecting melanoma in late or early stages?
4. What is the possible cost and outcome impact of teledermoscopy on early detection?
5. What is the possible impact on total costs using teledermoscopy for early detection of melanoma in Estonia?

The thesis consists of six chapters, chapter one being the introduction. Chapter two gives an overview of the relevant previous research and theory. The benefits of teledermoscopy and the impact of early diagnosis on treatment costs supported by literature is presented. Chapter three provides the methodology used to conduct the study and necessary

implementations and derivations of data. Chapter four presents the results of analysis. This is followed by chapter five where the results are discussed in correlation with previous literature and further suggestions are made. Finally, chapter six gives the conclusions of the study.

2 Background

2.1 Teledermatology

Dermatology – a very visual branch of medicine, is naturally suitable for modern telemedicine approach. Teledermatology involves taking digital image of the skin condition and the technology used for it may be different – images can be taken with digital camera (teledermatology) or dermoscope (teledermoscopy). Being able to store, process, and forward high-resolution images, teledermatology not only means an innovation in medicine but it is a method for increased effectiveness of care [13], [14]. The most important objective for implementing teledermatology is the possibility to offer patients special care via primary care level [2], [15].

Teledermatology can generally be divided into two major categories based on data transmission: store-and-forward (asynchronous) and real-time (synchronous) teledermatology [2].

Store-and-forward teledermatology stores patient medical information along with digital images. A healthcare specialist – a general practitioner, nurse, or a melanographer – sends the data to dermatologist at another location who then reviews the images of the skin and sends back the results. Based on the feedback from the dermatologist, the patient is asked to come for a follow-up in the future, referred to dermatologist visit, or if absolutely no abnormalities are found, no further action is taken [2]. The greatest advantage of this system is that the specialist does not have to be available at the same time the image is taken [15].

Opposite to store-and-forward, in real-time teledermatology, at least two parties have to be available for synchronous communication. Either video conferencing or phone calls can be used for that. The communication most commonly happens between a patient and a dermatologist. However, patient is often accompanied by a family physician or a healthcare assistant. Therefore, synchronous teledermatology requires more resources – both human and monetary – to be available [2]. The greatest advantage of real-time

system is the familiarity of it – the method imitates the traditional face-to-face care and increases the reliability of the consultation [15].

2.1.1 Teledermoscopy

Teledermoscopy is a subbranch of teledermatology. As said before, in case dermoscopic images are taken, the technology is called teledermoscopy. Epiluminescence microscopy, also known as dermoscopy, is a special non-invasive technique for viewing skin lesions in magnification *in-vivo* [16]. This technique uses immersion oil or spraying alcohol and a glass slide pressed to the skin [17]. It allows an early diagnosis as the incident light is absorbed – not reflected – from the surface of the lesion and the visualization of structures beyond the skin surface is possible [18]. As smartphones and other devices with internet connection have become so far-spread, mobile teledermoscopy is a logical improvement to offer an easily applicable solution because it reduces the need for special designated room for big equipment in the healthcare providers. Moreover, mobile teledermoscopy often allows a quick transmission of the image via special application [19].

2.1.2 Benefits of teledermosocpy

A study by Senel *et al.* [9] compared diagnosis and management plan of teledermoscopy to face-to-face evaluation. The researchers concluded that the reliability of diagnoses increased due to addition of dermoscopic images from kappa 0.77 to 0.85 and from kappa 0.75 to 0.86 for involved dermatologists A and B, respectively. The accuracy of diagnoses went from 85% to 94% and from 88% to 94% for dermatologists A and B, respectively. The reliability of management plans increased as well but the change was not statistically significant. Tan *et al.* [11] also compared face-to-face care to teledermoscopy in order to assess the diagnosis and management plan of patients who had been referred to dermatologist appointment. It was concluded that concordance between the decisions of face-to-face and teledermoscopy consultations were kappa 0.95 for both dermatologists. Also, results suggested that 75% of the referrals to the clinic could have been managed at primary care level. Based on histopathology, Coates *et al.* [10] reviews the accuracy of teledermoscopic diagnoses to range from 75% to 95%. Additionally, the accuracy increased by 15% compared to only using clinical images. A study by Massone *et al.* [19] compared face-to-face and mobile teledermoscopy diagnoses, being also the first study investigating mobile teledermoscopy. The diagnostic agreement among two

teleconsultants was concluded to be 89% for clinical images and 89-94% for dermoscopic images.

Börve *et al.* [20] compared mobile teledermoscopy to traditional paper-based referrals. The study concluded that waiting times for patients who needed surgery were significantly shorter. This includes waiting times both for the first dermatologist appointment and for the surgical procedure. Patients receiving teledermatology service (93.4%) were more likely to receive primary treatment in a single visit compared to paper referral cases (82.2%). Study also concluded that 99% of the images sent via teledermoscopy had satisfactory quality and could be used for diagnosing. Morton *et al.* [21] observed letter and teledermoscopy referral pathways. It was concluded that using teledermoscopy could reduce the need for dermatologist attendance at the clinic by 72%. Waiting times were also concluded to be shorter for teledermoscopy patients.

Based on previous literature, it can be concluded that teledermoscopy can have several benefits [9]–[11], [20]. Shorter waiting times [11], [20], [21] increase the probability of the patient getting to the doctor on time and receiving the medical attention needed. This means increased access to care. Therefore, having shorter waiting times results in earlier diagnosis and treatment that may directly affect patient's risk of premature mortality. What is more, the inclusion of dermascopic images is proven to increase the diagnostic accuracy when compared to usual face-to-face care where diagnosis is based on clinical images or observation [9], [10], [20]. The appropriate diagnosis can offer more effective management plan or avoid unnecessary visits to the clinic. Moreover, it has been found that the use of teledermoscopy could reduce secondary care visits by 72% [21]. This could possibly decrease the workload of dermatologists which in turn could result in higher patient satisfaction.

Shorter waiting times, better access to care and increased diagnostic reliability are the most important benefits teledermoscopy can offer for early diagnosis of melanoma. Voss *et al.* [22], concludes that early detection of melanoma increases the chances of patient survival, higher quality of life, and helps to decrease costs. Based on the US melanoma statistics, 84% of all new melanoma cases are localized, 9% regional, and 4% distant [5]. For Estonia, such statistics does not exist. However, according to the National Institute of Health Development, the relative survival rates for localized cancer are 99% and 93% for 1-year survival and 5-year survival, respectively. The 1-year and 5-year relative

survival rates for regional cancer are 91% and 59%. For distant melanoma, the 1-year and 5-year relative survival rates are 32% and 15%, respectively [23].

2.1.3 The differences to costs for using teledermoscopy

There have been previous studies and reports evaluating the costs of different stages of melanoma [24]–[26]. Based on national claims database, Reyes *et al.* [24] investigated the differences in melanoma treatment costs of patients with metastatic melanoma. The total healthcare costs for three different patient groups were on average 6773$, 10999$, and 15762$ per patient per month for lymph node metastasis, 1-3 metastases, and 4 or more metastases, respectively.

Alexandrescu [25] evaluated the cost of first 5 years of melanoma treatment in patients with different stages of melanoma. It was concluded that the overall cost of treatment significantly differs per tumour stage – being 4648$ for *in situ* melanoma and increasing to 159808$ for stage IV melanoma (Figure 1). Moreover, a comparison with other cancers, such as breast and colorectal cancer, indicated that melanoma is one of the most expensive cancers to diagnose, treat, and follow-up.

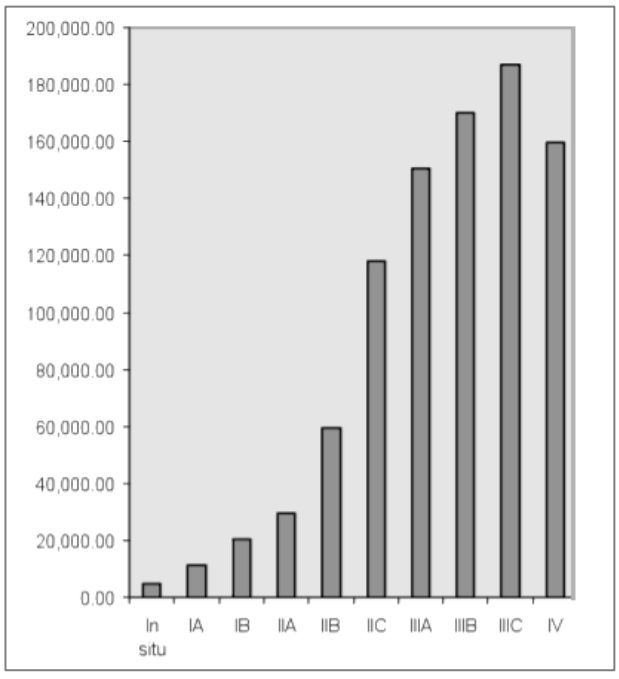

Figure 1. Melanoma overall costs ($) by clinical stage [24].

Styperek *et al.* [26] estimated the costs of different melanoma clinical stages based on 2008 national average Medicare reimbursements. The outcome indicated that the overall

cost of care for stage 0 was 72$ million and 199$ million for stage IV. When it was a recurrent stage IV, the total costs increased to remarkable 694$ million (Table 1). The costs per patient per year since diagnosis not surprisingly indicated that costs were highest for the first year of diagnosis, stage IV being 40 times more expensive that stage 0 melanoma in the first treatment year. Additionally, the incidence rates for melanoma clinical stages were presented to be 52.10%, 32.60%, 9.70%, and 5.60% for stages I-IV, respectively.

Table 1. 2008 cost of care by clinical stage for patients diagnosed with melanoma in a given year [26].

	Years since diagnosis & cost (millions)							
Stage	**1**	**2**	**3**	**4**	**5**	**6**	**7-10**	**Total**
in situ	$53.2	$4.1	$3.7	$3.0	$2.2	$1.7	$3.8	$72
I	$138.7	$10.9	$4.8	$1.9	$1.4	$1.1	$2.3	$161
II	$245.4	$15.9	$5.6	$0.9	$0.6	$0.5	$0.9	$270
III	$197.2	$36.1	$2.8	$1.3	$0.9	$0.2	$0.3	$239
IV	$147.0	$30.7	$7.4	$5.3	$4.8	$1.0	$3.2	$199

The systematic review by Guy *et al.* [27] reviewed articles that have evaluated direct costs of melanoma treatment. The previous research from the US, Europe, and other parts of the world were presented. The differences in costs of treatment by cancer stage were present in all studies. It was concluded that late-stage diagnoses of melanoma present a considerable economic burden. What is more, Seidler *et al.* [28] evaluated direct medical costs of melanoma treatment for patients aged over 64 and showed that when all melanoma patients would be diagnosed in an early stage (stage 0 or I), the annual treatment costs would be 40%–65% lower.

2.2 Economic evaluation in healthcare and telemedicine

In order to have better resource allocation, health economic evaluations are conducted. It is important that economic cost and effectiveness is assessed for every new addition to technology. These assessments of costs give the decision-makers understanding about the benefits, risks, and costs of interventions. Economic evaluations are applied in various healthcare areas, including prevention, diagnostics, treatment interventions, and rehabilitation [29].

2.2.1 Types of economic evaluation in healthcare

Economic evaluation is a comparative analysis of costs and consequences for alternative courses of action [30]. Economic evaluation in healthcare is a subpart of health technology assessment (HTA), which researches the impact that a possible technology has to economic outcomes [31].

There are several approaches concerning economic evaluations. For example, the Lewin group [32] has identified six different cost analysis types that can be used for telemedicine solutions. The specific method chosen depends on the particular intervention, its costs and outcomes and what is the purpose of the study.

The most basic method is cost analysis (CA). This approach focuses on costs (used resources and opportunity costs) of the intervention. It is the best option when it is not clear what benefits the intervention has or when one wants to compare several interventions that have different effectiveness. For example, when a project is in its early stages and the benefits have not been determined [33].

Similar to cost analysis is cost-minimization analysis (CMA) which is the most common type of economic evaluation. Supposing that the effectiveness of two or more interventions is the same, the costs are compared and the one intervention with the lowest resource expenditure is considered as the optimal choice. It is crucial to be careful concerning effects of interventions – these may seem similar at first but may significantly differ when all the factors are taken into account [33]. Therefore, it is suggested to apply CMA only if there is previous research on the equivalence of the interventions [30].

Cost-benefit analysis (CBA) – evaluates the intervention giving its benefits a monetary value. All benefits and all costs linked to an intervention are compared against each other. For that, benefit-cost ratio is used as an indicator that aims to evaluate the overall effectiveness. The greater the ratio, the better the investment is. Alternatively, the result could be presented in a form of a sum that represents the net benefit of one intervention over another [30]. For CBA it is not important that the effects of the interventions are equal, yet it is important that all outcomes can be expressed in monetary terms [33].

Fourth and fifth methods are cost-effectiveness analysis (CEA) and cost-utility analysis (CUA), respectively. CUA is the sub approach of CEA. These methods compare the costs

and outcomes of two or more alternatives. Unlike the cost-benefit analysis, outcomes are not given a monetary value. However, the presentation of costs is still done in a monetary value [32]. For the evaluation, cost-effectiveness ratio is used by dividing the associated costs of an alternative with an effectiveness measure, such as life year gained or clinical value (for CEA). Cost-utility analysis is a certain type of cost-effectiveness analysis where benefits are measured as a dimension of quality of life, i.e. either as quality-adjusted life-year or disability-adjusted life-year [33]. Compared to CBA, by default these two methods assume that one intervention is superior to another despite the net benefit. This may lead to undertaking an alternative that is not the most effective in monetary terms [30].

Additionally, one possibility for evaluation of healthcare programs is cost-consequence analysis (CCA). It differs from the methods discussed above and it is not so commonly used. This method does not determine a decision rule and displays costs and benefits in a disaggregated format. It is useful for obtaining whether an intervention has an impact or not. There is no weighting done and no ratios are calculated either – CCA relies on decision-makers judgment [32]. It draws on a fact that not all benefits can be measured in the same units and therefore cannot be combined into a single effectiveness measure [34]. CCA can be used as a sub approach of CEA where there are several output measures. In that case, an array of output measures is presented besides costs [30]. In this thesis, cost-consequence analysis will be used for economic evaluation.

Another approach in economic evaluation is using decision analytic modelling. There are two main structures – decision trees and Markov models. The more common decision model is decision tree that represents possible sequences by giving a series of pathways. Each pathway end point is assigned with values or pay-offs, such as QALYs or costs. The expected costs are then calculated by weighting the values/pay-offs by its respective probability and then summing across the possible pathways of an intervention. In Markov model, patients are assumed to occupy one of infinite series of health states at any given point of time. The model is run for a series of cycles during which patients make transitions between different health states, the speed of transition is determined by transition probabilities. The weighted expected costs and outcomes are then summed across the health states. Markov model could be used alone or in combination with decision trees [30].

For economic evaluation both – benefits and costs – of the healthcare intervention are important [35]. However, there may not always be clear costs and benefits that are, for example, easy to monetarise or fit into specific effectiveness measures. What is more, it may be more convenient and understandable for decision-makers to have health outcomes expressed separately rather than in some kind of combined value [36]. In the following two paragraphs, different types of costs and benefits are presented to support the method selection.

2.2.2 Types of costs

The input for economic evaluations are different costs – the ones that are rather apparent and others that are not that obvious. The costs used in economic studies can be divided into three main groups: (i) direct, (ii) indirect, and (iii) intangible costs. The hierarchy of costs can be seen in a figure below (Figure 2) [37].

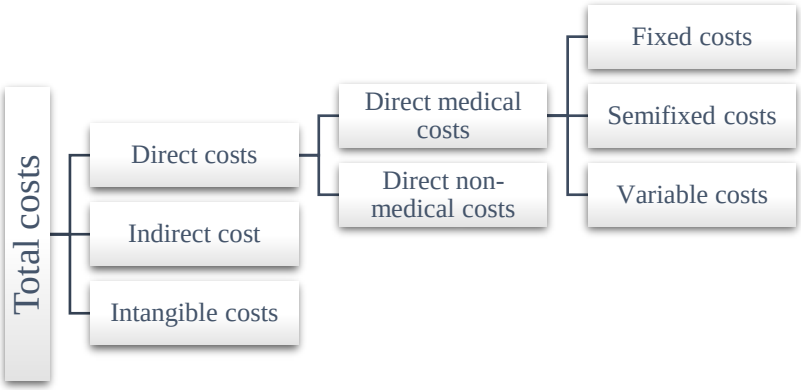

Figure 2. Types of costs used in economic studies [36].

Direct costs are those that are directly connected with healthcare intervention or illness. These costs can be divided in two – direct medical and non-medical costs. Direct non-medical costs are these direct costs that are not connected to the healthcare service itself, e.g. travelling costs for patients, disability pension payments. Direct medical costs include costs that are generated by the provided health service, i.e. costs of intervention and follow up in outpatient, inpatient, and nursing care, taking into account all specialist, including rehabilitation. To be more precise, direct medical costs can be divided into three: fixed, semifixed and variable costs. Fixed costs are costs that occur regardless of whether the patients are being currently treated or not. The majority of these are made up of capital and overhead costs, e.g. buying new equipment or paying for the internet

connection of the hospital. Variable costs – contrary to fixed costs – are directly dependent on the treatment of patients, e.g. disposable equipment, drugs. Semifixed costs are somewhat a combination of fixed and variable costs. When there is an increase in activity, fixed cost per unit decrease and variable costs increase in total. Semifixed costs increase only when there is a considerable increase in the level of activity – these costs stay fixed for a specific extent and undergo a steep rise after exceeding the range of activity level, e.g. nursing staff costs [37], [38].

Two other distinguishable types of costs – indirect and intangible – are not so straightforward and may be hard to financially quantify. That is the reason why those costs are not always considered when economic evaluations are carried out. Indirect costs are linked to the reduced productivity of the patient and their family/caregivers. This may be caused by the illness itself or its treatment and is highly dependent upon the certain health condition and its level of seriousness. Indirect costs may include reduced quality of life, reduced productivity at work, transportation to healthcare facilities, being absent from work. Compared to indirect costs, intangible costs are even harder to measure as they are naturally of non-financial nature. These costs may include stress or anxiety that is caused by the illness or its treatment, side-effects of the treatment, worry of the family of the patient [37], [38].

2.2.3 Types of benefits

Efficiency is achieved by maximizing benefits using the given resources. This means that when the amount of resources is limited, achieving one goal usually excludes the possibility to achieve the other. This is the concept of opportunity cost that is defined as the value of the benefits that are lost because the resources have been used to achieve a specific goal. Therefore, benefits and costs of the healthcare intervention should be compared in order to establish efficiency [35].

Benefits in economic evaluation of healthcare refer to the effect on the patient – the effect on service providers is not considered. To assess the benefits, different outcome measures are used. The main outcome measures are effectiveness, quality of life, utility, and monetary value given to certain benefit [37].

Effectiveness is the most straightforward and most commonly used benefit measure. It can be defined as a clinical indicator, such as number of pain-free days, reduction of

clinical symptoms, or as a more general outcome measure, such as life years gained, mortality, cases successfully diagnosed. Comparing clinical endpoints can be challenging as there may be more than one outcome reported for a specific treatment [39]. The more general and easy to measure outcome would be mortality. However, it can also be problematic as the death of a patient may occur due to different reasons, and many interventions target morbidity rather than mortality [37].

Quality of life (QoL) measures are special scales or surveys that can be divided into disease specific measures and generic measures. The first one focuses on certain symptoms of the disease and therefore makes it impossible to compare the results between different disease groups. The second one asks questions about patient's general health, for example pain, mental health, and vitality. This approach allows researchers to compare outcomes of patients with various diseases [37].

Utility measures are based on societal preferences, it is a numeric value a patient gives to a certain health outcome or state [39]. The interesting factor about utility measure is that patients value their conditions differently – some may put up with high levels of pain while others would not tolerate pain at all. This approach, similarly to generic quality of life measures, allows to compare different patient groups. Utility measure is based on interval scales allowing quantitative research. However, one has to be careful while using utility measures as they may be unresponsive to certain changes unless the sample size is really big [37].

Based on discussed, it can be seen that there are various types of costs and outcomes that depend greatly on the evaluation method used as well as the perspective from which the evaluation is done.

2.3 Previous research: economic evaluations in teledermatology

Teledermatology, like any other telemedicine field, is not yet a usual part of delivering care but is certainty an expanding area and therefore being researched further. There have been various studies done on teledermatology, its diagnostic accuracy and reliability, the costs and cost-effectiveness of the intervention. However, the topic is not enough analysed and it is certainty lacking long-term registry-based research. The articles being

reviewed are chosen based on a systematic review by Snoswell *et al.* from 2016 [12] that focuses on economic evaluations of store-and-forward teledermatology.

The articles reviewed [13], [21], [40]–[47] give a good overview of the research done concerning economic evaluation of teledermatology and its outcomes. All articles except for one used store-and-forward teledermatology and involved general practitioners as the one requiring the referral of dermatologist. A study by Parsi K *et al.* [46] used an online care delivery model that included patients taking their own images and communicating directly to a dermatologist via secured online transmission. Even though the basic outlook of the studies is similar, the methods and technology used for teledermatology still varied among studies. In most of the studies the skin condition of the patients was unspecified or expanded to any condition possible. There were three studies that focused on skin cancer patients, and one study that targeted psoriasis. Most of the studies used digital camera along with dermoscope. To forward these images, a server, intranet, or secure e-mail was used.

The study designs were rather similar. The most common method used to conduct the study was randomized controlled trial (RCT). This was followed by prospective observational study and retrospective observational study, respectively. As the RCT is considered as a gold standard in clinical research, allowing researches very specifically control the setting of the study and minimize the bias, real-world studies should not be underestimated concerning economic evaluations as they offer a large population, long timeframe and flexibility [48]. In all studies, there were two groups of interest: intervention and control. Intervention group attended store-and-forward teledermatology appointments and control group received traditional face-to-face care after being referred by the general practitioner. The sample sizes varied from rather small (64 patients) to a large registry sample (37207 patients). However, most of the sample sizes were somewhere in a range of 200–600 participants.

The majority of the studies were conducted from the perspective of the third-party payer and only two studies had taken the societal perspective. Therefore, most of the studies did not consider loss of productivity, travel times and out-of-pocket expenses in their cost identification. Outcome measures of the studies where effectiveness was evaluated were QALYs, number of referrals, or waiting time to the dermatologist. The type of economic evaluation was determined in most of the studies. However, in some studies analysis type

was not specified or – even worse – the described method and actual analysis did not exactly match. Almost all economic evaluation types were represented – cost-minimisation analysis being the most used method followed by the cost-effectiveness analysis. In many studies, uncertainties were not addressed by carrying out sensitivity analysis.

The overall conclusion of the conducted studies was that store-and-forward teledermatology is cost-effective when this helps to reduce the need for traditional dermatologist appointments. Yet, there were two studies [40], [41] that concluded that teledermatology and conventional referral system are equivalent concerning cost-effectiveness. As far as costs were analysed, all the studies except for two [41], [47] found that using teledermatology helps to somewhat reduce the total costs of care process per patient, but the savings were not remarkable. Sensitivity testing indicated that cost-effectiveness of teledermatology is often dependant of waiting times and travelling costs.

Based on the previous research, there seems to be a level of uncertainty concerning the study conclusions of the economic analysis. The final results were often dependent of other factors, such as the inclusion of travelling costs. Also, teledermatology system and equipment were mainly determined irrelevant concerning the cost identification. It can be concluded that even though in most studies teledermatology was proven to be cost-effective, the actual costs themselves did not significantly differ between the interventions. What is more, in two studies [40], [41] teledermatology and conventional care were concluded to be equivalent. Therefore, the main effectiveness was determined by the benefits teledermatology offers, e.g. shorter waiting times, and not so much because of the difference in actual costs.

2.4 The gap in research

Time to initial intervention was used as a measure of effectiveness in many studies, but the effect of early diagnosis was not considered. Thus, there is a gap in literature regarding the benefits of teledermoscopy in terms of actual cost reduction of melanoma treatment due to early detection of the disease. As studies showed, costs of teledermatology process depend on the specific healthcare context and not so much of the intervention used.

In most studies, images were taken using digital camera rather than dermoscope. Therefore, researchers were not considering the additional benefit that dermoscopic images offer compared to images taken with digital camera. What is more, most of the studies were really short in terms of time horizon and there lacks real-world evidence of melanoma treatment trends in terms of costs and the distribution of costs over the course of treatment.

2.5 The scope of the study

In general, the fields under research are economic evaluations and telemedicine. In this thesis, economic evaluations are further narrowed down to a specific mode of economic evaluation – cost-consequence analysis. Additionally, because telemedicine affects both health outcomes and costs, a possibility to reduce costs by early detection of melanoma was brought into investigation by teledermoscopy service. Therefore, the intent of this thesis is to address the benefits and costs of teledermscopy process based on previous literature, as well as analyse the real-world data from Estonian Health Insurance Fund (EHIF) to determine the costs of melanoma diagnosis and treatment based on medical bills from 2006 to 2016. The patients included in the study population were diagnosed with malignant melanoma (ICD-10 C43) and/or melanoma *in situ* (ICD-10 D03) during the mentioned 11-year interval. Cost-consequence analysis is used because it gives the overall list of benefits and costs. Displaying the impact as extensively as possible allows decision-makers to only consider the most relevant aspects [36].

It is important to point out that this study discusses two very different types of costs. The costs regarding teledermoscopy as a similar intervention to a face-to-face dermatologist visit, and the cost of diagnosis and treatment of melanoma of which reduction could be regarded as a benefit of teledermoscopy.

3 Methodology

3.1 Overview of the study design

3.1.1 Study design

Figure 3. Study design.

3.1.2 Choice of methods

A retrospective registry-based study including patients with malignant melanoma is conducted. Based on the data entered to EHIF registries during years 2006–2016 a cost-consequence analysis is carried out in order to evaluate the effectiveness of teledermoscopy in melanoma treatment.

Since there is no precise data concerning outcome measures, the effectiveness is presented based on previous research. Thus, cost-consequence analysis method is used because it allows to present the outcomes alongside the costs in a disaggregated format without requiring one combined effectiveness measure. The use of cost-consequence analysis

therefore offers decision-makers a more approachable and understandable presentation of the study conclusions [36].

The demographic features of the patients are presented using summary statistics. Categorization of the patient data is done based on deaths, gender, age, and diagnosis. To answer the research question 1, the costs associated with diagnosis and treatment of melanoma are determined using summary statistics and visualised per year with the proportions of health service categories. To answer the research question 2, patients are divided into two subgroups – early and late detection. Since it is not possible to obtain information regarding the stage of melanoma from EHIF data, the derivation is done based on literature and expert interviews in order to distinguish patients between late and early detection of the disease (see paragraph 3.2.2). The costs are then compared and described using summary statistics. To answer the research question 3, a what-if analysis is carried out in order to evaluate the possible impact of early detection on costs of diagnosis and treatment of melanoma. In order to describe the relationship between early detection and total costs, the proportion of early stage detection will be increased by 1%, 5%, and 10%.

The formula used for evaluating the difference is

$$\Delta_{costs} = costs - \left[\bar{x}_{early} \cdot p \cdot \left(r_{early} + i\right) + \bar{x}_{late} \cdot p \cdot (r_{late} - i)\right],$$

where

- Δ_{costs} is the difference in costs;
- $costs$ is the total sum of melanoma treatment costs;
- $\bar{x}_{early}$ and $\bar{x}_{late}$ are the sample means of subgroups;
- p is the total number of patients in the sample;
- r_{early} and r_{late} are the current percentages of patients in subgroups;
- i is the change, $i = 1\%, 5\%, 10\%$.

To answer the research question 4, a literature review based of previous research is done to determine the impact of teledermoscopy on early detection. Research question 5 is answered with a discussion based on the results of questions 3 and 4.

The selection of early detection impact is an estimate based on studies by Styperek *et al.* [26] and Alexandrescu [25]. As the actual increase in early detection depends on a number of factors regarding the actual implementation of teledermoscopy, then the author does not propose an actual number of possible impact, but rather shows what kind of impact could the extent of implementation have on the total costs of melanoma treatment. In simple words, should teledermoscopy be made highly accessible and supported, it could have a higher effect on early detection due to accessibility of dermatologist opinion and therefore have an impact on total melanoma treatment due to decrease of late stage treatment cost.

3.2 Description of data

The data concerning the cost of melanoma treatment was obtained from EHIF. The author received anonymous data regarding demographic information of patients, diagnoses, medical bills, and health services.

In the database there are in total of 5830 patients who have either malignant melanoma of skin (ICD-10 C43) or melanoma *in situ* (ICD-10 D03) among their principal or secondary diagnosis during the years 2006–2016. The study population includes all 5830 patients in the database. However, the inclusion and exclusion criteria was applied to medical bills based on whether or not it was possible to determine any direct reference to melanoma-related services, for example surgical procedures of the skin. As a result, there were 2613 patients with no direct evidence to melanoma treatment. For these patients, medical bills only from the first year of diagnosis were kept as the patient could have turned to private healthcare after their diagnosis. Patients with metastatic melanoma and all the medical bills concerning their treatment were not excluded from the study as the metastases are the result of the late detection of melanoma.

The key variables used for analysis were:

- Demographic variables:
    - Anonymous patient ID;
    - Age group;
    - Region;
    - Gender;

    - Year of death;
- Medical bills:
    - Medical bill number;
    - Start date of the bill;
    - End date of the bill;
- Health services:
    - Health service code;
    - Category of health service.

Anonymous subject IDs are 8-digit codes assigned by EHIF in order to protect the identity of the patients. No permit was requested from Estonian Data Protection Inspectorate. Therefore, the demographic data is displayed as general as possible. For the age of the patient (at the time of the diagnose), 10-year intervals are used: 0–9, 10–29, …, 80–89, 90–99 and concerning the death date of the patient, only year is displayed. The region indicates the place of residence of the patient. The final dataset includes patients from 15 different foreign countries. As the proportion of such patients is insignificant (0.50%), they were not removed. Also, for some patients the information regarding the region is missing.

Start and end dates of the medical bill express the interval during which the services, such as treatments and investigations, were rendered. Each medical bill has listed the exact codes for the services the patient received. These codes were nominated price and category of service based on the list of health services [49] for the health insurance fund. Exceptions were primary care services where funding is based on general practices. For these services where either health service code was completely missing or the service was categorised as general practitioner appointment, the missing costs were imputed (see paragraph 3.2.1).

3.2.1 Imputation of cost for general practitioner appointments

In Estonia, general practitioners have a gatekeeper role which means that specialized care can only be reached through general practitioners with the exception of dermatology and gynaecology care. The planning and management of primary care access is done by the Health Board, most of the contracting and resource channelling of general practitioners

and nurses is done by EHIF. Every family doctor has a service area determined by the Health Board and maintains a practice list from 1200 up to 2000 patients [50].

The providers in Estonia have monthly payments that are combination of age group adjusted capitation, fee-for-service payments that cover minor surgery and gynaecological procedures that a family doctor can perform, and a Quality Bonus Scheme. Also, Estonian general practitioners have additional allowances for premises, transport, and for servicing in remote areas [51].

Based on Estonian Health Insurance Fund Yearbook 2016 [52], the actual budget of 2016 was summed and an average per practice list was calculated: 128677.06€ per list. The average number appointments of both family physician and family nurse per list was approximately 7397. Thus, it may be concluded that the average cost of one appointment is 17.4€. All the data used for the calculation, can be seen in a table below (Table 2).

Table 2. Imputation of the average cost of general practitioner appointment [52].

Service	**Cost**
Appointments of the family physician	4595989
Appointments of the family nurse	1336312
Number of lists	802
Basic allowance	*9816000*
Distance allowance	*464000*
Second family nurse allowance	*5259000*
Total capitation fee	*61144000*
Fee for Services fund	*22091000*
Operations fund	*529000*
Therapy fund	*716000*
Performance pay	*2237000*
Allowance for appointments during non-working hours	*341000*
Family physician advisory line	*602000*
Total yearly budget	103199000
Average cost of one appointment	17.4

3.2.2 Derivation of early and late detection of melanoma

In 2013 EHIF procured an audit [53] on melanoma diagnosis and treatment in Estonia. The target group of this audit were patients who had gotten melanoma diagnosis as their principal or secondary diagnosis during the year 2012 which in total meant 453 patients. In the audit, the sentinel lymph node biopsy (SLNB) was considered as an important prognostic factor for survival.

SLNB is a special procedure that is supposed to determine whether the melanoma cells have spread to the sentinel nodes. In case of draining of the tumour from its primary tumour site, sentinel lymph node is usually the first one where the cancer cells are likely to spread. SLNB has been confirmed to be a minimally invasive prognostic tool with a high value and it is believed that is the most specific staging tool currently available [54]. What is more, it is a recommended method by American Joint Committee on Cancer that purposes an internationally accepted melanoma staging system in its Cancer Staging Manual [55].

In this thesis, SNLB is considered as a key procedure that is used as an indicator of late detection of melanoma. According to the study by Han *et al.* [56], 70% of new cases are thin melanomas (melanomas with Breslow thickness ≤1 mm) in which case the survival rates are over 90%. However, it is suggested that SLNB should be indicated when the melanoma is >0.75 mm in Breslow thickness. Forsea [54] advises to perform SLNB mostly for tumour stages I and II. The melanoma treatment audit of Estonia also states that SLNB is not required in case of *in situ* (stage 0) melanoma. As discussed above (paragraph 2.1.3) the share of costs for *in situ* cases is considerably lower than for the later melanoma stages.

Based on an interview with an oncology resident, additional indicator for late detection of melanoma is used. For circumstances when it is already known that the tumour has spread to the lymph nodes (stage III) or distant organs (stage IV) and sentinel lymph node biopsy is not performed, skin, bone, and soft tissue chemotherapy is used as an indicator.

Therefore, taking into consideration previous literature and an expert interview with oncology resident, categorization of melanoma patients is defined as follows:

- Early detection of melanoma: patients with no SLNB or chemotherapy among their medical bills;
- Late detection of melanoma: patients with SLNB or chemotherapy among their medical bills.

The categorization was applied to all 5830 patients. There were in total of 982 (16.84%) patients who had sentinel lymph node biopsy, 107 (1.84%) patients who had chemotherapy among their medical bills, and 89 (1.53%) patients had both procedures – SLNB and chemotherapy – among their medical bills. The distribution based on which year of patient's treatment the procedure occurred is given in the table below (Table 3). Thus, based on this data one can show that the share of early detection (no prognostic factor of late detection) of melanomas was 79.79%. This is about 15% more than the stated share of early stage melanomas as shown by Padrik et al. [53]. The difference may be caused by the fact that in the audit, the early detection was defined as melanomas with less than 1 mm Breslow thickness or melanoma *in situ*.

Table 3. Frequencies of procedures based on patient's treatment year.

Treatment year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
SLNB (%)	86.98	9.02	1.67	1.21	0.65	0.19	0.19	0.00	0.09
Chemotherapy (%)	32.65	32.65	13.27	12.24	4.59	1.53	1.53	1.53	0.00

It can be seen that 87.02% of sentinel lymph node biopsies are done within the first year of patient's treatment, 9.02% are done during the second year, and the remaining 4% are done during the following years. Out of other lymph node biopsies, 56.8% were done within the first and 26.61% during the second year of treatment. 65.30% of patients received their first chemotherapy session during the first two years of the treatment, 13.27% during their third year and 12.24% of patients received it for the first time during their fourth treatment year. Based on literature [57] and an expert interview, it can be concluded that the real-world data supports using sentinel lymph node biopsy and skin, bone, and soft tissue chemotherapy as suitable indicators for the categorization of early and late detection of melanoma.

3.2.3 Costs

Based on data from EHIF database, the types of cost considered are direct medical variable costs, i.e. the costs of intervention and follow-up in outpatient, inpatient, and nursing care that are directly dependent on the treatment of patients. Other direct costs, i.e. fixed costs, direct non-medical costs, indirect, and intangible costs are not considered in this thesis as they are not recorded on medical bills. Because of that, costs such as out-of-pocket payments for the patient, cost of medical equipment, cost of loss of income, costs of incapacity to work and disability benefits are not taken into consideration. Therefore, the cost analysis is done from the health service perspective only.

The costs in the database have been divided by EHIF into following categories: anaesthesia, bed days, blood and blood products, complex services (Diagnosis-Related Group based), family doctor visits, laboratory test, medicinal products, outpatient visits, surgeries and accessories, tests and procedures, and other costs, such as rehabilitation. All costs were updated to EHIF prices in year 2016.

3.3 Method quality control and limitations

3.3.1 Ethical considerations

For the data analysis, primary delicate personal data was used. As it is a retrospective registry-based study, there was no informed consent. Also, no permit was requested from Estonian Data Protection Inspectorate. The confidentiality of the patients was ensured with anonymous subject IDs and displaying only general demographic information.

3.3.2 Limitations

The economic evaluation carried out has its limitations. Firstly, the quality of the secondary data from EHIF database is dependent on collection and coding of data at the service level. There is always human factor present when inserting for example diagnose codes. Secondly, the sensitivity analysis was not carried out in a rigorous form. For testing the inputs, what-if analysis was used instead. Due to the fact that cost-consequence analysis does not require sensitivity analysis because a model is not built [32], [37]. However, that particular limitation is not as crucial because the same assumptions can be made with the what-if analysis as an input to further research. Thirdly, the economic evaluation did not consider the societal perspective due to lack of relevant information.

Also, only the costs available on medical bills were included in the analysis. The societal perspective acquires including all the costs and outcomes of the intervention, regardless to whom they apply – including indirect and intangible costs [37]. Therefore, due to challenges discussed in paragraph 2.2.2, true societal perspective is hard to achieve [37].

4 Results

4.1 Descriptive results

4.1.1 Demographics

In total, 5830 patients were included in the study population. The basic demographic and clinical features of the patients can be seen in a table below (Table 4).

Table 4. Demographic and clinical features of the patients.

	Patients
N	5830
Age	60
Sex	
Female	3783 (64.89%)
Male	2047 (35.11%)
Diagnosis	
C43	4705 (80.70%)
D03	1462 (25.07%)
Death	1431 (26.60%)

Out of these 5830 patients, the biggest age group at the time of diagnosis was 70–79 (22.92%) that was followed by 60–69 (19.37%) and 50–59 (15.71%). The youngest patients belonged to age group 0–9 (0.26%) and the oldest to 90–99 (1.42%) (Figure 4). The estimated mean age at the time of diagnosis was 60 and estimated median age 63.

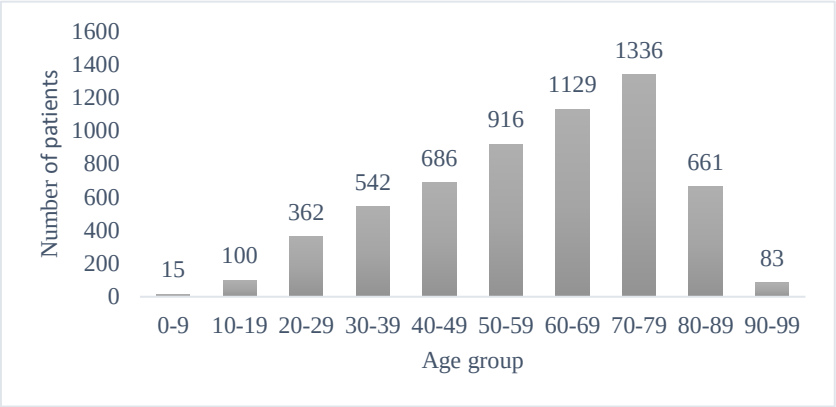

Figure 4. Melanoma patients by age group.

Most of the patients (80.70%) had diagnosis of malignant melanoma of skin (ICD-10 C43) and a smaller group of patients (25.07%) had diagnosis of melanoma *in situ* (ICD-10 D03). The total of two groups was higher than 100%, due to the fact that there were 337 (5.78%) patients having both diagnosis during their treatment period.

There were notably more females (64.89%) than males (35.11%). However, the estimated mean age did not differ between the genders, being 61 and 59 for men and women, respectively. Also, diagnose proportions did not significantly vary either. However, there was a notable difference between deaths of men and women. While 45.63% on all deaths were men and 54.37% were women, the overall death rate among men was 31.90% and among women it was more than 10% lower – 20.57%. The overall mortality increased with the increase in age group. The difference between mortality rates concur with national cancer registry data.

The melanoma patients are distributed all over Estonia. The biggest number of patients – 2506 (45.19%) – come from Harju county. This is followed by Tartu county with 684 (12.34%) and Ida-Viru county with 572 (10.32%) patients. The least patients come from Hiiu county with 45 (0.81%) patients. There are three patients whose region is marked as Estonia and 285 patients do not have their region specified. Additionally, there are in total of 29 patients out of which 20 are from Finland and the rest from Sweden, Denmark, Germany, the United Kingdom, Belarus, and Russia.

4.1.2 Early and late detection

The derivation for creating two subgroups – early and late detection of melanoma – is described earlier in the thesis (paragraph 3.2.2). As a result of applying indicators based on literature and an expert interview, 5830 patients were divided into early detection group with 4652 patients (79.79%) and late detection group with 1178 patients (20.21%). The basic demographic and clinical features of the patients can be seen in a table below (Table 5).

Table 5. Demographic and clinical features of patients of early and late detection.

	Early detection	**Late detection**
N	4652	1178
Age	59	61
Sex		
Female	3075 (66.10%)	708 (60.10%)
Male	1577 (33.90%)	470 (39.90%)
Diagnosis		
C43	3528 (75.84%)	1177 (99.92%)
D03	1390 (29.88%)	72 (6.11%)
Death	1018 (21.88%)	413 (35.06%)

In early detection group, the biggest age group at the time of diagnosis was 70–79 (23.09%) that was followed by 60–69 (17.93%) and 50–59 (14.66%). The youngest patients belonged to age group 0–9 (0.32%) and the oldest to 90–99 (1.68%). The estimated mean age at the time of diagnosis was 59 and estimated median age 63.

In late detection group, the biggest age group at the time of diagnosis was 60–69 (25.04%) that was followed by 70–79 (22.24%) and 50–59 (19.86%). The youngest patients belonged to age group 10–19 (0.17%) and the oldest to 90–99 (1.68%). The estimated mean age at the time of diagnosis was 61 and estimated median age 62.

The differences between the subgroups can be seen in a figure below (Figure 5). There is a slight difference in age distribution between early and late detection. In early detection group, there are more patients at the both ends of the distribution and the biggest number of patients belonged to age group of 70–79 at the time of diagnosis. On the other hand, in

late detection group patients are more mature and the biggest number of patients belonged to age group of 60–69 at the time of diagnosis. However, estimated mean and median are both similar within the subgroups.

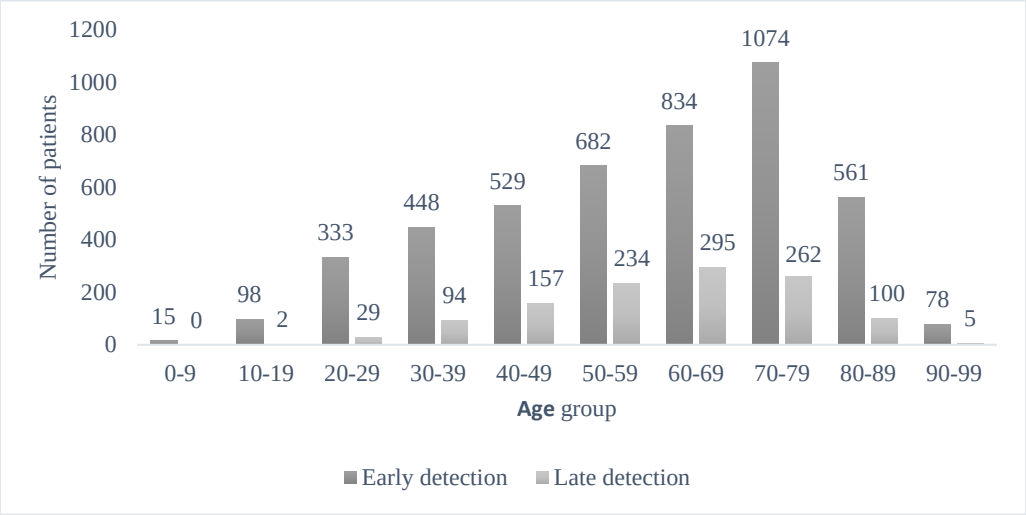

Figure 5. Melanoma patients of early and late detection by age group.

In early and late detection groups, the distribution of men and women was more or less similar. The percentages were 66.10% and 60.10% for females and 33.90% and 39.90% for males in early and late detection group, respectively. Therefore, the proportion of men in late detection group increased by 6% when compared to early detection.

There were notable differences between two subgroups concerning diagnosis and mortality. In late detection group, all patients (99.92%) except for one had diagnosis of malignant melanoma of skin (ICD-10 C43). Additionally, 71 patients had diagnosis of melanoma *in situ* (ICD-10 D03) as well. There was one patient who only had melanoma *in situ* diagnosis but was assigned to late detection subgroup because of the SLNB. However, performing SLNB to a patient with melanoma *in situ* is contradictory. In early detection group, three quarters of patients (75.84%) had diagnosis of malignant melanoma and a third of patients (29.88%) had melanoma *in situ* diagnosis. There were 265 patients who had both diagnoses.

The distribution of deaths in subgroups can be seen in the figure below (Figure 6).

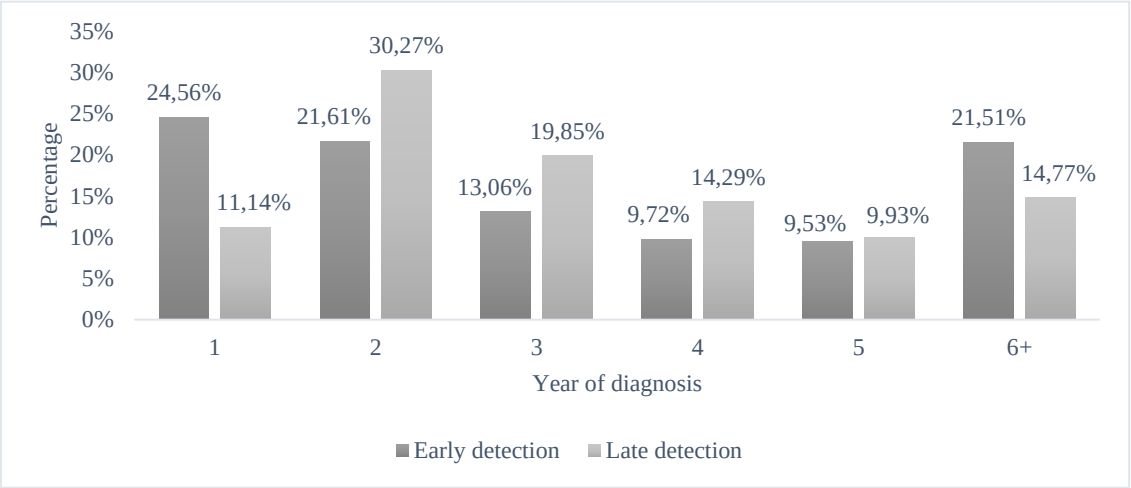

Figure 6. Distribution of deaths by the year of initial diagnosis.

The overall death rate in early detection group was 21.88%. Most deaths occurred during the first (24.56%) and second (21.61%) year of diagnosis. Also, remarkable percentage of deaths (21.51%) occurred after five years of diagnosis. Comparing the deaths in early detection group between genders, men had higher mortality during the first years of the diagnosis while the great amount of deaths of women occurred after 5 years of diagnosis. The overall death rate in late detection group was 35.06%. The biggest amount of deaths (30.27%) occurred during the second year of diagnosis and only 11.14% of deaths occurred during the first year. The differences between genders were similar to early detection group.

4.2 Cost analysis

The overall costs have been changing along with the change in the number of patients as can be seen in a figure below (Figure 7). During the 11-year interval, costs and the number of patients each year have nearly doubled. The total cost in 2006 were 794005€ and in 2016 had this number risen to 1499899€ (Appendix 1).

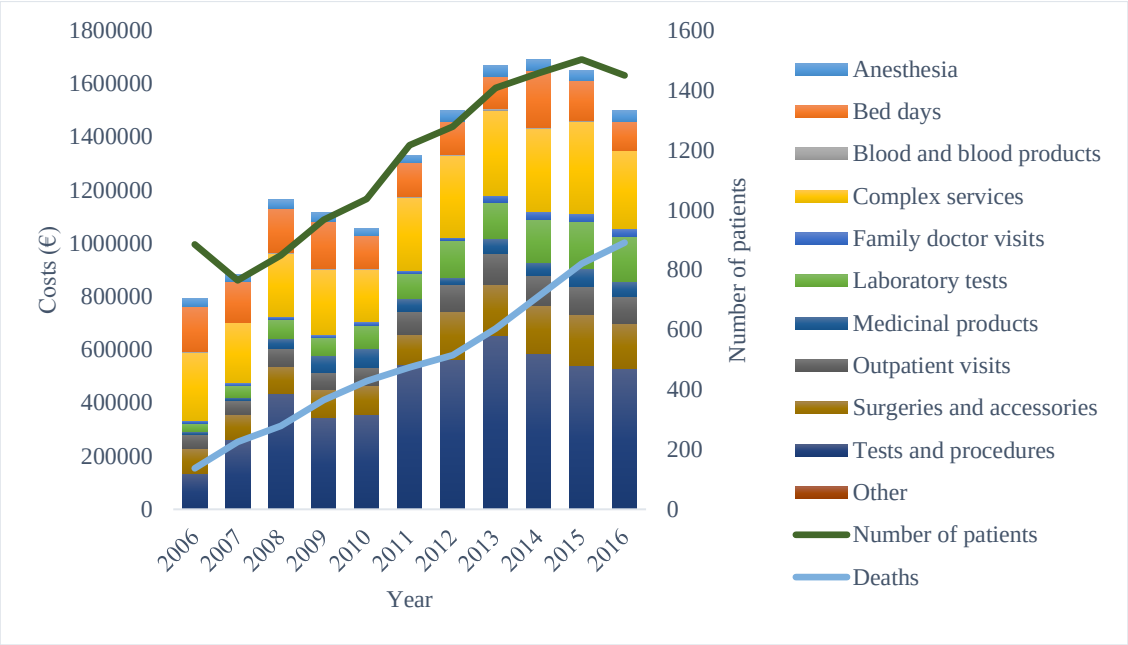

Figure 7. Costs of melanoma diagnosis and treatment by year.

The number of patients has gone from 885 in 2006 to 1450 in 2016. There has been a slight increase concerning the annual costs per patient, in 2006 the average cost per patient was 897.18€ which raised to 1034.41€ in 2016. Concerning the portions of early and late detection there has been a small rising trend of early detection.

The biggest share of all costs went to tests and procedures (34.48%) that was followed by complex services (20.95%), bed days (11.44%), and surgeries and accessories (10.62%). The smallest share of costs went to family doctor visits (1.36%), blood and blood products (0.26%), and other healthcare services (0.05%).

In the figure below (Figure 8), the 11-year average melanoma costs by the treatment year are given. It can be seen that the first-year treatment costs are significantly higher than in the following years, being by average 7833854€. The second-year treatment costs were already 62% lower with 268134€, the third-year costs were 76% lower with 170114€ and the decrease in treatment costs continued with each treatment year and was 18006€ by the eleventh year of diagnosis.

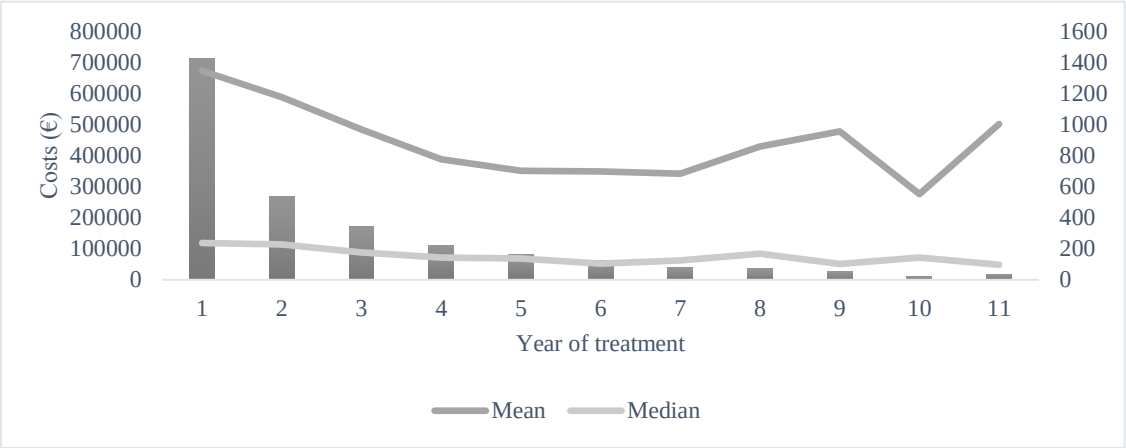

Figure 8. 2006–2016 average costs (€) by treatment year.

The mean and median values of per patient per treatment year varied less between the treatment years. The mean value for the first-year treatment costs was 1343.71€ and median 236.57€. The second-year mean and median were 1173.45€ and 227.28€, respectively. These numbers continued to follow the downward trend with the few exceptions caused by the small number of patients whose treatment lasted for so long. Therefore, the mean value was more dependent on extreme values for these treatment years. The distribution of patients based on the length of their treatment (expressed in years) is shown in a table below (Table 6).

Table 6. distribution of patients by treatment length.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Early detection	3371	437	248	185	143	127	67	32	24	8	10
Late detection	174	263	183	164	118	117	62	54	21	14	8
Total	3545	700	431	349	261	244	129	86	45	22	18

When comparing the treatment costs between late and early detection, notable differences can be seen (Table 7). The first-year treatment costs are high in both subgroups – 3057361.09€ and 4776492.91€ in early and late detection group, respectively. However, the costs decrease in early detection group after the first treatment year while in late detection group the decrease in treatment costs is slower. The total sum of treatment costs in late detection group is about two times higher than in early detection group while the number of patients in late detection group is four times less than in early detection group.

Table 7. Costs of treatment for early and late detection in a given treatment year.

	Year of treatment	Sum of costs	Mean	Median
Early detection	1	3057361.09	657.21	85.15
	2	853524.73	666.30	140.23
	3	435095.93	515.52	112.49
	4	220990.88	370.79	101.97
	5	143493.61	349.13	101.09
	6+	243434.30	440.21	88.26
	Total	4953900.54	594.21	102.07
Late detection	1	4776492.91	4054.75	3752.86
	2	1827816.64	1820.53	546.83
	3	1095929.29	1478.99	384.02
	4	672276.02	1204.80	288.93
	5	420573.72	1067.45	230.29
	6+	608156.40	1005.22	188.15
	Total	9401244.99	2098.49	619.01

The mean and median values per patient per treatment year emphasize the differences in costs between two subgroups even more. The first-year mean treatment cost in early detection group is 657.21€. However, the median value (85.15€) of the same treatment year indicates that the mean value is probably affected by some extreme treatment costs. The mean value decreased and median increased for the following treatment years, the overall mean value of a treatment year was 595.21€ and median 102.07€.

The first-year mean treatment cost in late detection group was much higher (4054.75€) compared to early detection. What is more, the median is also high with 3752.86€ which indicates that in this subgroup, the mean value is less affected by extreme costs and treatment of the patients in late detection group is much more expensive. The mean cost lowers with each treatment year but still remains higher than in early detection group. The overall mean value of a treatment year was 2098.49€ and median 619.01€.

As the costs in early detection group varied greatly within treatment years, the costs of patients who died (1018 patients) were removed from this group to see the possible change in costs. It was assumed that melanoma may have been more aggressive for these patients. Additionally, for patients who only had skin-related procedures at the beginning of their treatment, the medical expenses from the following years were excluded. It was assumed that melanoma was diagnosed very early and there is a probability that the costs form the following years may not be related to melanoma treatment. The adjusted costs for early detection group can be seen in a table below (Table 8).

Table 8. Costs of treatment for adjusted early detection in a given treatment year.

	Year of treatment	Sum of costs	Mean	Median
Early detection	1	1872020.83	515.14	72.17
	2	373549.86	864.70	318.64
	3	217371.40	668.84	201.07
	4	102784.27	393.81	137.69
	5	76263.61	361.43	125.67
	6+	124115.66	377.25	107.67
	Total	2766105.63	532.76	107.67

It can be seen that the total summed costs of the first treatment year decreased by almost 50%. Mean and median values also indicate the reduction in extreme treatment costs. The total sum on costs went from 4953900.54€ to 2766105.63, the mean value and median were 515.14€ and 72.17, respectively.

4.2.1 What-if analysis of total costs

In order to evaluate the possible cost saving from having more patients diagnosed in the early stage of melanoma, a what-if analysis was carried out using the formula described in paragraph 3.1.2. Based on the results from Table 5 and Table 7, the average cost per patient is 1064,90€ and 7980.68€ in early and late detection group, respectively. The total sum of melanoma treatment costs was 14355145.52€. The results of increasing the percentage of early detection by 1%, 5%, and 10% can be seen in a table below (Table 9).

Table 9. Potential savings when increasing early diagnosis.

	1 %	**5 %**	**10 %**
Total costs	13953635.71	12340874.32	10324922.58
Costs reduced	401509.81	2014271.20	4030222.95
Average saving per year	36500.86	183115.60	366383.90
Percentage saved	2.80%	14.03%	28.08%

It can be seen that when everything else remains the same, increasing the number of patients in early detection group helps to reduce the costs of melanoma treatment. Changing the proportion of patients only by 1%, it is possible to reduce the costs by 2.80%. Average per patient total saving would be 68.87€ for 1% change, 345.50€ for 5%, and 691.29€ for 10% change.

Based on the results from Table 5 and Table 8, the average cost per patient was 761.17€ and 7980.68€ in early and late detection group, respectively. The total sum of melanoma treatment costs was 12167350.62€. The result of applying what-if analysis to a study sample where deaths and irrelevant medical costs of early detection group have been removed can be seen in a table below (Table 10).

Table 10. Potential savings when increasing early diagnosis (adjusted early detection group).

	1 %	**5 %**	**10 %**
Total costs	11819947.82	10430336.62	8693322.63
Costs saved	347402.80	1737014.00	3474027.99
Average saving per year	31582.07	157910.40	315820.70
Percentage saved	2.94 %	16.65 %	39.96 %

Changing the proportion of patients only by 1%, it is possible to reduce the costs by 2.94%. Average per patient total savings would be 72.20€ for 1% change, 360.98€ for 5%, and 721.95€ for 10% change.

5 Discussion

The present retrospective registry-based study using EHIF data of melanoma skin cancer from years 2006–2016 investigated the significance of early detection of melanoma. The demographic baseline results of melanoma indicate that the average melanoma patient is 60 years old when first diagnosed and there is a higher probability that the patient is rather female than male. During the time interval of 11 years, both – patient numbers and deaths – have increased quite rapidly. While the overall mortality indicates the higher number of deaths of women because there are more females in the study population, the mortality of men is notably higher. Similar trend can be seen in international cancer statistics as well [7], [58]. A study conducted by Whiteman *et al.* [8] assessed the current melanoma trends in the US, Australia, New Zealand, the UK, Sweden, and Norway and aimed to project future incidence rates of melanoma. It was concluded that the overall numbers of melanoma patients will increase in the following years.

When demographic indicators were looked more in detail between patients in early and late detection group, a notable difference can be seen. Out of all females, 18.71% were determined to late detections group and the same percentage for males was 22.96%. Therefore, the higher mortality rate among men could be explained by the possibly lower overall awareness that results in later detection of melanoma. About one third of deaths in late detection group occurred on patients' second year of diagnosis. Mortality stayed quite high for the third year of diagnosis but showed a decreasing trend. Contrary to that, in early detection group, one fourth of deaths occurs on the first year of diagnosis. This may indicate that early detection group also includes patients with more aggressive cancer. Mortality is also high for the second year but decreases after that. What is more, a large proportion of deaths occurred six or more years after the diagnosis that implies the possibility that these deaths may not all be directly related to melanoma. The patients in late detection group are slightly younger, although the estimated median ages were almost the same.

Concerning the costs of melanoma treatment, it was demonstrated that patients whose melanoma was diagnosed in an early stage, had notably lower treatment costs. The

treatment costs of melanoma have increased over the years as the number of patients has increased. The greatest share of money is spent on different tests and procedures that include for example ultrasonography and computed tomography. Another big share of money goes to complex services that include for example skin surgeries. The size of medical bills of patients were found to be very different that caused mean and median values to differ greatly.

When the costs of two subgroups were compared, the differences were excessive. The mean costs per patient of the first-year treatment were 657.21€ and 4054.75€ in early and late detection group, respectively. For both subgroups, the first year of treatment was the costliest in terms of sum of all costs after which there was a decrease of costs with each treatment year. Similar aspect was reported by Styperek *et al.* [26] who evaluated the year 2008 cost of care for melanoma in the US. In late detection group, where about 40% of patients die within the first two years after diagnosis, it may be assumed that there are high end-of-life expenses related to melanoma treatment. The overall costs of early detection were two times smaller than the costs of late detection. When additional assumptions were applied to early detection subgroup, the difference in costs increased even more – the mean cost per patient of the first-year treatment was 515.14€ and median cost 72.17€. As a result, there was a three-time difference between early and late stage melanoma treatment costs. In comparison, Styperek *et al.* [26] reported almost three-times difference between the total treatment costs of *in situ* (stage 0) and stage IV. Alexandrescu [25] concluded in his study that stage IV melanoma cancer is 34 times more expensive to treat compared to melanoma *in situ*.

Increasing the proportion of patients in early detection group by 1%, 5%, and 10% showed a possible cost saving for melanoma treatment. Hence, even a small percentage of additional early diagnosis could help lessen the economic burden of melanoma treatment. In 2011, Department of Health in the UK published an economic modelling project [59] that aimed to assess the likely impact of earlier diagnosis of cancer on costs and benefits. It was found that melanoma costs increase from stage I to stage IV and by early diagnosis it would be possible to have a reduction in treatment costs. Considering the benefit of life-years gained, early detection of melanoma was concluded to be cost-effective. Therefore, also taking into account the findings of Whiteman *et al.* [8] and the

increasing trend of melanoma cases in Estonia, there is an urgent need to promote primary prevention and early detection.

Estonian melanoma audit [53] pointed out that the time it took for a patient from initial dermatologist appointment to surgery was unacceptably long. However, due to technical reasons, it was not possible to evaluate the time from registration to initial dermatologist appointment. According to EHIF [60], the maximum allowed waiting time for specialised medical care is six weeks (30 days). The most recent statistics from year 2018 indicate that the average waiting time for dermatologist in Estonia is currently 44 days, the shortest waiting times are in Ida-Viru county (1 day) and the longest in Hiiu county (97 days). Contrary to that, maximum waiting time for family doctor is five working days. According to a study [61] procured by EHIF and Ministry of Social Affairs in 2016, it was found that the biggest problem for patients concerning the healthcare system are long waiting times for specialised medical care. It was also concluded that 64% of people visited their family physician at least once during the year and 70% of people aged 60–74 visited their family physician three or more times during the year. Based to EHIF data, the estimated median age of patients who were diagnosed with melanoma was 63. For that reason, making a shift from specialised care to primary care using teledermoscopy should be considered for early detection of melanoma.

According to previous research [9]–[11], [20], [21], it has been shown that teledermoscopy offers increased access to care and increased diagnostic reliability. Therefore, promotes early detection of melanoma. Previous literature that has been investigating teledermoscopy (or teledermatology) service user acceptance and/or satisfaction have concluded that it is important for patients to receive fast and high-quality care [62]. For example, Whited *et al.* [63] found that patients had no clear preferences for the type of consultation but were satisfied with teleconsultation 82% of the time. Also, it was reported that teledermatology offered more timely referrals for patients. Coates *et al.* [3] concludes that the satisfaction of teledermatology is as high as conventional face-to-face care as it provides shorter waiting times and increased access to care in rural regions.

Considering everything mentioned above, there is a great opportunity for teledermoscopy to promote early detection of melanoma skin cancer. As a trend of increasing patient numbers were detected from EHIF data as well as from international research [8], innovation in this area is needed to have more effective diagnosing. The costs of

melanoma treatment were found to greatly vary between early and late detection – two- to three-time difference was detected. When early detection could be increased by 1%, the reduction in overall costs could be 2.80% (in total of 401509.81€, average annual saving 36500.86€), when early detection could be increased by 10%, the reduction in overall costs could be 28.08% (in total of 4030222.95€, average annual saving 366383.90€). As teledermoscopy is found to be a reliable diagnostic tool offering shorter waiting times [9]–[11], [20], [21], it could be successfully used for early detection of melanoma.

The desired level of detail could only be achieved by receiving the data from EHIF database in a deconstructed form and all the pieces of information had to be put together manually. Doing so, the author of this thesis encountered some issues. Firstly, during the years of interest (2006–2016) Estonian kroon was replaced with euro. However, there was no information concerning the currency and whether the conversion was done automatically by the system or not. This uncertainty was eliminated as the list of health services for the health insurance fund was used to nominate the medical costs. Secondly, the information of recurrent diagnosis was not evaluated due to assumed randomness in coding techniques. Thirdly, family doctor visits often did not have a service code and the date of occurrence was missing. For these records, the date of medical bill could be used. Nevertheless, the overall data quality was satisfying and the author did not come across any major data errors.

For future research, it is recommended to collect information about the cancer stage at EHIF level. This would enable more accurate further research concerning the characteristics and costs. Estonian Cancer Registry collects specific information regarding cancer cases, for example tumour grade, extent of disease, and cause of death. This specific data would add value to economic evaluations. Therefore, further research should be done about the possibilities to connect EHIF data to cancer registry data.

The assumptions made in this paper concerning the early and late detection could also be further specified. For that the clinical care activities distinctive for different melanoma stages as well as for different stages of treatment should be mapped. Also, this additional information would allow to evaluate the treatment compliance with international guidelines. The similar technique of early and late detection could be used by researchers and EHIF to evaluate early detection impact of other cancer types and help to focus

prevention activities. Additionally, the evaluation of other and unspecified malignant neoplasms of skin (ICD-10 C44) could be made based on the findings of this thesis.

6 Conclusion

The aim of this thesis was to evaluate costs of melanoma diagnosis and treatment and investigate the possibility of decreasing costs by increasing early detection with using teledermoscopy in Estonia.

The results of this thesis provide important information regarding the topic of interest. Firstly, the costs of melanoma diagnosis and treatment in Estonia have been increasing with each year as there is an upward trend regarding patient numbers. Similar trend has also been reported in international statistics making it even more important to diagnose melanoma as early as possible.

Secondly, the treatment cost differences between early and late detection group are notable. The difference between the subgroups was found to be 2-3 times concerning the overall treatment costs. The greatest differences were found to be during the first treatment year where average treatment costs per patient in late detection subgroup were quite enormous. The findings were supported by previous research where treatment costs have been also concluded to be dependent on cancer stage.

Thirdly, the what-if analysis of costs suggests that by increasing the proportion of early detection patients, it is possible to decrease the overall spendings. Even a small change towards more effective diagnosing would have an impact on treatment costs.

Fourthly, based on previous research, it was concluded that teledermoscopy increases the availability of care. What is more, the use of dermoscopic images has been found to increase the diagnostic reliability and accuracy. Therefore, having increased access to care and more precise diagnosing, teledemoscopy could be used as a supportive tool to promote early detection.

Finally, taking into account all the findings, it can be concluded that by increasing the use of teledermoscopy as a supportive tool for diagnosing, it can have a positive effect on early detection due to accessibility of dermatologist opinion and therefore, reduce the overall costs of melanoma treatment by lowering the burden of late stage treatment costs.

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Appendix 1 – Melanoma treatment costs in 2006–2016

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	All years
Anesthesia	30998.98	27895.31	32046.94	33416.61	28923.16	29666.92	40098.52	40764.07	39020.04	40116.41	42671.78	**385618.74**
Bed days	171122.13	153033.93	166834.63	177717.64	124168.01	126374.39	126619.63	122987.44	215990.61	147592.28	108559.06	**1640999.75**
Blood and blood products	1730.30	1372.70	3682.28	3320.74	4197.71	3105.22	3800.26	6107.41	4410.30	4278.63	1978.47	**37984.02**
Complex services	256253.12	226611.71	236886.54	245558.91	195300.29	274716.58	305144.55	318171.28	310218.45	345937.80	291474.27	**3006273.50**
Family doctor visits	10109.40	10718.40	10196.40	11031.60	12789.00	11518.80	11501.40	26256.60	28884.00	32642.40	29562.60	**195210.60**
Laboratory tests	32339.35	43362.68	71847.40	66233.60	86035.96	95543.97	142147.40	138410.60	162114.24	174985.48	171126.37	**1184147.05**
Medicinal products	11780.40	13490.46	37141.61	65901.18	72066.28	45930.73	26514.95	53970.25	48858.54	67601.74	53998.04	**497254.18**
Outpatient visits	51463.99	51831.70	67092.19	63415.27	69436.50	86352.29	100662.05	117742.45	114151.16	105418.24	100961.65	**928527.49**
Surgeries and accessories	93275.23	91798.02	104155.71	104123.73	106035.21	113832.72	178249.91	192143.59	178900.16	191763.31	170004.40	**1524281.99**
Tests and procedures	134932.43	261992.86	433184.09	344221.66	357639.91	544358.15	563784.29	652688.81	586151.97	539440.88	529562.84	**4947957.89**
Other	175.18	1653.30	767.73	864.50	428.43	361.38	610.31	199.50	724.14	833.59	272.25	**6890.31**
TOTAL	**794005.33**	**882107.77**	**1163067.79**	**1114940.94**	**1056592.03**	**1331399.77**	**1498522.96**	**1669242.50**	**1688699.47**	**1649777.17**	**1499899.48**	**14348255.21**