ERASMUS UNIVERSITY ROTTERDAM
Erasmus School of Economics

Cost-effectiveness analysis of the genotyping-based treatment for ER+ breast cancer patients treated with tamoxifen

Master Thesis
Health Economics

Jade Hendriks
Student number: 579782

15th June 2021

Supervisor
Dr. Erwin Birnie

Second reader:
Dr. Max Coveney

Word count: 16804

Abstract

This Master's thesis contributes to the cost-effectiveness of a pharmacogenetic (PGx) Passport. The specific study elaborates on a PGx application in the treatment of certain breast cancer patients with the drug tamoxifen. Tamoxifen is included in the PGx-Passport because of strong indications of genetic factors, i.e. the presence of certain gene polymorphisms, that influences the patient's response to the drug. Economic evaluations of genotyping-based tamoxifen treatment are currently lacking, which in addition to clinical evidence is essential before it can be applied in practice. The study was conducted to answer the following research question: *"What is the cost-effectiveness of the genotyping-based treatment for women with ER+ early breast cancer treated with tamoxifen in the Netherlands compared to the standard of care?"* The PGx-strategy in which patients with a CYP2D6 'slow metabolizer' polymorphism receive a twofold tamoxifen dose increase (40mg/day during 5 years) is compared to the standard treatment (20mg/day during 5 years). A model-based cost-utility analysis was performed for women with an initial age of 50 years who were prescribed tamoxifen, from a societal perspective with a lifetime horizon. The PGx-strategy results in additional costs both for genotyping the CYP2D6-enzyme and for the increasing tamoxifen dose. This increase is offset by the cost reduction mainly associated with a lower number of breast cancer recurrences when applying the PGx-strategy. The results suggest that the PGx-strategy is highly likely to be cost-effective compared to the current standard care (ICER: -€16,719/QALY gained). In most cases, this will be cost-reducing intervention and dominant over the standard of care, i.e. more effective (+0.34 QALYs gained) and less costly (-€5,701). The ICER is most sensitive to the health state utilities and costs of treating recurrences. Probabilistic sensitivity analysis (PSA) indicates that the cost-effectiveness's probability was 94% at a WTP of €0 per QALY and 95% at a societal WTP of €20,000 per QALY. Several assumptions were made for this cost-effectiveness study. However, PSA shows that the assumptions do not impact the ICER substantially. The model results are considered valid, reliable and robust. Healthcare professionals and healthcare policymakers are advised to implement PGx information in daily routine care. However, the introduction of the PGx Passport into routine care will not only depend on cost-effectiveness considerations; It poses several other challenges, most importantly the proper and ethical use of an individual's genetic information. This is expected to be the subject of a broad social debate.

Acknowledgement

This Master's thesis is an excellent addition to my studies in Health Economics at the Erasmus University Rotterdam (School of Economics) and a great extension to my previously obtained Master degree in Business Economics at the University of Antwerp (Belgium). The research described in this thesis has given me the opportunity to gain more knowledge about the fascinating subject of pharmacogenetics. Researching this topic gave me a great feeling of working on something exciting and challenging that will impact and improve our future healthcare system. I learned a lot during the process of conducting a cost-effectiveness analysis related to pharmacogenetics. Without the help of several people, I would not have been able to deliver this Master's thesis in its current form. Therefore, I would like to express my thanks to several persons.

I would like to thank my supervisor, dr. Erwin Birnie. I am grateful for his guidance, patience and constructive feedback throughout the process. He has fascinated me with his knowledge of conducting cost-effectiveness analyses. Building a Markov model and finding the necessary input parameters was challenging, and I was unfamiliar with it. Dr. Erwin Birnie guided me well in this step by step and always gave me good advice. Several meetings with my fellow student, Janou Kempkens, were also useful, and I learned a lot from her experience working on the same subject. Thank you very much for the excellent cooperation!

Finally, I would like to thank my family and friends for their unconditional support and encouragement during this period. Writing a thesis is an intensive process and doing this for the second time – after conducting a thesis in Antwerp – scared me initially. But thanks to their involvement, I experienced this as a lovely, exciting and highly motivated period.

A sincere thank you to all!

Table of contents

List of Figures

List of Tables

1. Introduction

Medicines enter the market after approval by regulatory authorities. However, drugs are rarely effective in 100% of the patients to whom they are prescribed (1). Many drugs have an optimal effect in only 25-60% of patients (2). Besides protocol adherence (by practitioners) and treatment compliance (by patients), side effects and ineffective or less effective treatment for specific patient subgroups may occur (3). Most treatment protocols assume a 'one-size fits all' approach, but some people need higher or lower doses of a drug to achieve the same therapeutic effect. Also, when the medication has no or little effect, a different drug may be recommended (1,4).

Literature increasingly focuses on genetic factors that determine an individual's response to drugs (5). Pharmacogenetics - here used synonymously with pharmacogenomics - analyses how an individual's genetic make-up affects the response to a specific drug (6). The field of pharmacogenetics is a fundamental component of 'precision medicine' or 'personalized medicine' (4,5,7). Discovering genetic alterations that influence the patient's response to drugs is central to pharmacogenetics (6). The aim is to use this information in order to personalize and optimize treatments, considering the patient's genotype, which improves the efficacy and/or safety of medicines and reduces the costs associated with adverse events or less effective or ineffective treatments (4-9). Nowadays, the 'Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie' (KNMP) lists about 50-60 drugs for which there is a strong indication of an interaction between the drug response and the presence of certain gene polymorphisms and for which clinical guidelines are available (10). The number of drugs with gene-drug interactions is expected to increase significantly (1). Pharmacogenetic tests are available to test for either the presence or absence of a relevant gene when a specific drug is prescribed, or to test for multiple genes in one run (e.g. by whole genome sequencing) so that the genetic data can be stored and used later in life (11). With this second pre-emptive panel-based strategy, a 'pharmacogenetic passport' (PGx-Passport) can be developed that contains a large amount of an individual's genetic information. Based on the PGx-Passport, treatments throughout the patient's life could be optimized and thus benefit the patient (11). Samwald et al. estimate that half of the patients over 65 years will use at least one of the

drugs for which PGx guidelines are available in four years (12). In addition, a quarter to a third will use two or more of these medicines (12).

Despite clinical evidence of drug-gene interactions and the benefits of PGx testing, the question of whether it should be used in routine care remains a challenge (6,13). Several challenges are observed, including the interpretation by qualified professionals (genetic counsellors, general practitioners, pharmacists) and ethical questions about the use of personal genetic information (3). Moreover, the cost-effectiveness of PGx testing should be investigated to support the prioritization of health care spending and societal decision making, i.e. strengthen the treatment recommendations for healthcare professionals and healthcare policymakers on whether PGx should be used and reimbursed in routine care (14,15). Relatively few economic evaluations have been conducted in the current literature for genotyping-based treatments (4,14,15).

The current study will elaborate on the cost-effectiveness of one pharmacogenetic application in the treatment of certain breast cancer patients with the drug tamoxifen, that is included in the PGx-Passport.

Cancer is the leading cause of death in the Netherlands (16). The term cancer describes a heterogeneous group of disorders with the common characteristics of uncontrolled cell growth and cell dissemination (1). Abnormal (malignant) cells are formed that can invade adjacent tissues (tissue invasion) and spread through the blood and lymphatic systems to other parts of the body, a process called metastasis (1). The cause of developing cancer is often unknown; it may be due to, among others, exposure to radiation or chemical substances, an unhealthy lifestyle, or hereditary predisposition (17). Cancer is a severe disease that is usually fatal if left untreated (17). Cancer treatment is constantly improving as new technologies and treatment strategies are developed (6). Recently, the determination of somatic gene mutations – mutations that arise throughout life – in tumor tissue is increasingly used to guide (personalized) treatment (6,18). In recent years, there has also been great interest in the role of inherited (germline) mutations in optimizing the treatment of cancers and thus moving towards a broader ‘personalized medicine’ or ‘precision medicine’ (6).

Breast cancer is the most common cancer in women in the Netherlands; about one in seven women will develop breast cancer at some time in life (19,20). A total of 13,200 women were newly diagnosed with breast cancer in 2020 (1.5 per 1000 women) (20). 88% of female breast cancer patients are still alive 5 years after diagnosis, and about 3,000 people annually die from breast cancer (19,20). In 2017, healthcare expenditure for breast cancer totaled €870 million in the Netherlands (20). Breast cancer patients undergo curative surgery (breast-conserving therapy or mastectomy) to remove primary cancer (including affected adjacent lymph nodes) (21,22). Surgery is often combined with adjuvant treatments such as radiotherapy, chemotherapy, biological therapy and/or hormone therapy (21,22). Advances in early detection - due to the national breast cancer screening program in the Netherlands for women aged between 50-75 years - and adjuvant treatment of breast cancer have led to a significant reduction in breast cancer recurrence and breast cancer mortality (21,23). Traditionally, only clinical and histopathologic factors are used to guide the choice of therapy (6). These factors include tumor stage, tumor size, nodal status, and intra-tumoral characteristics such as grade, expression of estrogen and progesterone receptors (ER+, PR+, triple-negative), and HER2 (human epidermal growth factor receptor 2) status (6).

Two-thirds of breast cancers are estrogen receptor (ER+) positive (6,24). ER+ breast cancer may be treated with adjuvant hormone therapy (endocrine treatment) - after primary therapy - that blocks specific receptors, preventing or inhibiting tumor growth (6). Tamoxifen (TAM) and aromatase inhibitors (AI) anastrozole, letrozole and exemestane are the most commonly used drugs in endocrine therapy to prevent breast cancer recurrence (6,21,22,24,25). TAM and AI both disrupt estrogen signaling, but they have different mechanisms of action (6); the selective estrogen receptor modulator TAM blocks the estrogen receptor, while AI blocks the pathway (by inhibiting the aromatase enzymes) through which estrogen is produced (6). TAM has shown a higher incidence of thrombotic events and endometrial cancer, whereas AI treatment leads to a greater risk of cardiac events and fractures caused by increasing the risk of osteoporosis (26,27). Tamoxifen has been the standard adjuvant hormone treatment for more than 50 years, prescribed to women with ER+ early breast cancer (6). Research suggests that 5-year treatment of TAM reduces the risk of breast cancer recurrence by approximately 40% and the risk of mortality by approximately 30% compared with those receiving no

hormonal therapy (23). Tamoxifen during 5 years improved the results – breast cancer recurrence and breast cancer mortality - compared to 2-year TAM treatment (22,28).

Nowadays, in the Netherlands, TAM combined with AI is recommended for postmenopausal women with ER+ breast cancer (22), as several studies indicate better efficacy of this strategy (27,29,30). Therapy consists of sequential treatment with 2 to 3 years of TAM followed by 2 to 3 years of an AI (or the reverse order). If there is a contraindication for one of the two drugs, treatment for 5 years with the other drug is the alternative. For premenopausal women with ER+ breast cancer, TAM during 5 years remains the standard of care (AI is not effective for this subgroup) (22).

Although TAM is proven to be an effective adjuvant treatment (23), wide variability in the response of individuals to TAM when administered at the same doses is observed (25,26). This variable efficacy of TAM treatment remains a clinical challenge (23). Interindividual genetic variations in the CYP2D6 liver enzyme, the major metabolic pathway to convert the prodrug TAM into its active metabolite, may contribute to this response variability (25,26). CYP2D6 belongs to the superfamily of cytochrome P450 (CYP450) enzymes which play an important role in the metabolism of a significant proportion of all medicines, both in the breakdown of regular drugs as in the activation of prodrugs (31,32). Many polymorphisms in the CYP2D6-enzyme (>80) are identified and vary across populations (26,33,34). For some variants, the impact on enzymatic activity is determined (34). CYP2D6*4 is the most prevalent polymorphism in the Dutch population, with an incidence of around 18% (26,34). CYP2D6 mainly metabolizes the prodrug TAM into its active metabolite 4-hydroxytamoxifen, which is 30-100x more potent compared to TAM. CYP3A4/5 further converts this metabolite to endoxifen. Endoxifen is also produced by hydroxylation of the N-desmethyl-tamoxifen metabolite by CYP2D6 (22). Based on a patient's CYP2D6 genotype, patients can be classified as CYP2D6 slow metabolizers, normal metabolizers or rapid metabolizers (26). Slow metabolizers - patients with deficient alleles - are expected to have lower CYP2D6 metabolism rates, leading to little or no therapeutic benefit when receiving a standard dose of the prodrug TAM (22,25,26). The association between CYP2D6 genotype and TAM response is widely discussed in the literature (25,26,35,36). Several clinical studies have shown a significant association between CYP2D6 'slow metabolizer' polymorphism and reduced TAM efficacy,

with an increased risk of breast cancer recurrence for slow metabolizers (37-39). Other studies, however, failed to demonstrate a significant association (40-42). KNMP and FDA (US Food and Drug Administration) recognize TAM for an association between genetics and the drug response (10,43). Although suggestive clinical evidence exists, testing for this enzyme polymorphism is not yet implemented in daily practice to optimize an individual's adjuvant hormone treatment. Economic evaluations of TAM treatments based on CYP2D6 genotyping for ER+ breast cancer patients are currently lacking, which, as mentioned earlier, is essential before it can be applied in practice (26).

In this study, a cost-effectiveness analysis will be conducted to compare TAM treatment based on a patient's genetic profile with the standard of care to contribute to the effectiveness to treat ER+ breast cancer in the Netherlands.

In the Netherlands, ER+ breast cancer patients with a genetic variant that codes for a reduced CYP2D6 metabolism rate - slow metabolizers - are recommended to either select an alternative treatment to TAM or to increase the TAM dose (44). For premenopausal women, a 1.5-2-fold increase in the standard dose of TAM is the preferred option (44). For postmenopausal women, either the same dose increase can be used or alternative treatment with only aromatase inhibitors during 5 years can be chosen (44).

Studies have examined the relationship between the CYP2D6 genotypes and the variation in outcomes (mortality and breast cancer recurrence) for the standard therapy in the Netherlands for postmenopausal women (2-3 yrs TAM + 2-3yrs AI). Although a significant effect was found between the CYP2D6 genotypes in the first 2-3 years of TAM, this was no longer significant after it was followed by aromatase inhibitors (45). This means that the variation in efficacy of TAM is outweighed when it is followed by AI. Therefore, the option of an alternative treatment with AI monotherapy for CYP2D6 slow metabolizers treated with TAM followed by AI (standard care for postmenopausal women) will not be investigated in this study. On the other hand, clinical studies examined the relation between CYP2D6 genotypes and the outcomes for hormone therapy with 5 years TAM. Several studies observed significant differences between the genotypes, mainly in the likelihood of breast cancer recurrence (37,38). In the Netherlands, both postmenopausal women with a contra-

indication for AI and premenopausal women generally receive monotherapy with TAM (22). An alternative treatment with aromatase inhibitors (5yrs AI) for patients with CYP2D6 polymorphism is not effective in the majority of this subgroup (premenopausal women) (44). Therefore, the option of increasing the TAM dose depending on the genotype is central to this thesis. Increasing the TAM dose by a factor of 1.5-2 for slow metabolizers – CYP2D6 polymorphism - in women receiving 5 years of TAM treatment significantly increases endoxifen levels to reach similar concentrations as in the patients without the genetic variant, resulting in similar therapeutic outcomes (45-48).

Therefore, this study will focus on women with ER+ early breast cancer receiving 5 years of adjuvant TAM treatment, in which women with the CYP2D6 'slow metabolizer' polymorphism receive a twofold TAM dose increase (40mg/day) instead of the standard dose of 20mg/day, and compare the results with 5 years of standard adjuvant TAM treatment. All Dutch patients receiving tamoxifen for 5 years are the population of interest in this study, i.e. postmenopausal women with a contra-indication for aromatase inhibitors and premenopausal women. The study objective is to assess the cost-utility of the pharmacogenetic-guided hormone therapy (genotyping-based strategy) for women with ER+ early breast cancer receiving tamoxifen for 5 years compared to tamoxifen treatment without genetic information, from a societal perspective, using a lifetime horizon. This study is relevant for societal reasons, as to maximize patient benefits and reducing costs for the healthcare sector due to ineffective treatment with tamoxifen for ER+ breast cancer. The cost-effectiveness analysis will contribute to the economic literature on breast cancer treatment in ER+ women using PGx testing to support decision making on the use of the PGx-passport in daily routine care.

The research question is:

"What is the cost-effectiveness of genotyped-based treatment for women with ER+ early breast cancer treated with tamoxifen in the Netherlands compared to the standard of care?"

The following sub-questions are formulated:

1. What are the health effects of the genotyped-based treatment strategy and current standard of care strategy?
2. What are the costs of the genotyped-based treatment strategy and the standard of care strategy?
3. What is the incremental cost-effectiveness ratio (ICER)?
4. To what extent is the ICER uncertain when changing input parameters? (sensitivity analysis)
5. What are the conclusions for decision making on pharmacogenetic testing in routine care?

The remainder of this thesis will be structured as follows: Chapter 2 elaborates on the background of the pharmacogenetics concept and the framework for the economic evaluation; Chapter 3 describes the methodology to conduct the cost-utility analysis; Chapter 4 presents the results; finally, Chapter 5 includes the discussion relevant to the findings, limitations, implications and an overall conclusion.

2. Theoretical framework

2.1. Background pharmacogenetics

2.1.1. Genetics

Humans are different from each other because of their unique genetic make-up (1). Nucleic acids provide the genetic material of cells (1,49). They carry the instructions that allow cells to function as they do and to divide, thus enabling the growth and reproduction of living organisms. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are the two main classes of nucleic acids (49). DNA molecules consist of a double helix structure with a specific sequence of nucleotides (1). The nucleotides are composed of deoxyribose-phosphate and nucleobases (adenine (A), thymine (T), guanine (G) and cytosine (C)) (1). The specific sequence of nucleotides forms a code in which, among other things, the hereditary properties are laid down (1). DNA is found in cells in the form of chromosomes, a large DNA-protein complex. An individual's entire genetic code – all the different DNA molecules – is defined as the 'genome'(1). A piece of DNA that codes for a certain characteristic – information for the formation of a protein - is called a gene (1). A gene can occur in different versions, called alleles (i.e. genetic variations) (50). The genetic information is passed on to successive generations of cells through cell division. A distinction can be made between genotype (i.e. a set of characteristics inherited by the parents) and phenotype (i.e. a total of all observable characteristics) (1). So, genotyping is a process of identifying differences in individuals' genetic make-up by examining the individual DNA sequence. Changes in DNA code, called mutations, frequently occur during cell division (replication of DNA) and are called somatic mutations. When these mutations are present in reproductive cells (oocytes and spermatozoids), they are called germline mutations and thus are inheritable. Genetic variation and these changes in the DNA sequence between generations contribute to the inter-individual variation in the genetic make-up, causing that every individual is unique (1,50).

2.1.2. Genetics in drug response

Genetic factors may contribute to the individual response to drugs besides physiological factors, environmental factors and lifestyle factors (51). Various genetic factors account for 20%-95% of the individual variability in drug response (52). Human genetic variation occurs when one or more nucleotides are altered: switched, inserted, or deleted (53). The alteration of one nucleotide - single nucleotide polymorphism (SNP) - is the most common type of DNA sequence variation (7). In other words, genetic variation describes differences between DNA sequences of individual genomes (1), which can be inherited (germline gene variants) or arise throughout life (somatic gene variants) (1,53). Pharmacogenetic testing mainly focuses on the first source: germline genetic variation present in the patient since birth (53).

Pharmacogenetics focuses on how the genetic variability, due to molecular alterations at the level of drug-metabolizing enzymes, drug targets/receptors, and drug-transport proteins, influence the efficacy and the safety of drugs for individuals (1,8). The aim is to detect in the DNA these changes that can affect the individual response to medication. The main two determinants that are central to individual variability in drug response are pharmacokinetics (PK) and pharmacodynamics (PD) (6,8). Genetic alterations might affect the function or expression of proteins involved in these processes (6). PK defines what the body does with and to the drug (encompassing ADME: drug absorption, distribution, metabolism and excretion). PD concerns the drug's mechanism of action at the level of receptors, enzymes or ion channels (54), so it determines how the person is affected by the drug. Both together influence dosing, benefit, and adverse events of drugs (1).

Current pharmacogenetic literature is mainly focused on the impact of genetic variation on the expression and function of drug-metabolizing enzymes (PK). Much less is known about the pharmacogenetics of drug target/receptors and drug-transport proteins (8), which is also less relevant for the application in this thesis. Therefore, these last categories will not be discussed further.

Every drug that enters the body - taken orally or intravenously - must be absorbed, distributed, activated (in case of a prodrug), reach its target, perform its action and be

inactivated or eliminated (1,7). Prodrugs differ from 'regular' drugs; prodrugs are inactive drugs that require metabolic activation (i.e. converted in the body) into an active drug (active metabolite) to be effective (1,53). Genetic factors play a role in the variation between individuals in drug metabolism at each of these levels. Drug metabolism is the metabolic breakdown of drugs for regular drugs detoxified by metabolism, usually through specialized enzymatic systems (54). Most metabolic processes take place in the liver and intestines (7). Drugs work optimally when the drug concentration in the blood is between a specific range (therapeutic window) (1). If the drug concentration is below this therapeutic range, the benefit might be insufficient (drug underdose); if above this range, there is an increasing risk of toxicity (drug overdose) (1). The ability to break down medication is regulated by an individual's metabolism, which can vary between individuals, affecting both drug efficacy and safety (1). Genetic alterations can lead to the absence of or altered enzyme activity (54). The corresponding phenotypes (expressed characteristics like metabolic capacity) to the different genotypes (genetic make-up) are usually classified into four major groups (8,53):

1. *Poor metabolizers (PMs)* have a risk of overdose or side effects due to the accumulation of the drug in the body because they have a genetic variant that codes for a defective metabolizing enzyme.
2. *Intermediate metabolizers (IMs)* have a genetic variant that codes for a reduced enzyme function and therefore exhibit similar, but less severe, problems as PMs.
3. *Extensive metabolizers or normal metabolizers (EMs or NMs)* have normal enzyme activity, which allows them to obtain the expected response to a drug.
4. *Ultra-rapid metabolizers (Ums)* show an increased enzyme activity resulting in a limited or no therapeutic response to the drug.

In the context of this thesis, it is important to note that with prodrugs (such as tamoxifen) – which need to be activated by certain liver enzymes – it is the opposite effect (53). Slow metabolizers (which, for simplicity, are assumed in this thesis to be both PMs and IMs) have little or no therapeutic benefit at a normal drug dose since the drug will be less activated. Rapid metabolizers (Ums) have a higher exposure to the active metabolite resulting in a risk of overdose since the prodrug activation proceeds efficiently.

2.1.3. Current evidence on pharmacogenetics

Friedrich Vogel is credited with first coining the term “pharmacogenetics, i.e. the role of genetics in drug response” in 1959 (55). More recently, pharmacogenetic research has expanded as a result of the tremendous amount of genetic data generated by the Human Genome Project (HGP) (8). The HGP was the international research effort to determine the DNA sequence of the entire human genome (56). The interest in associations between genes and drug response is increasing (1). Several pharmacogenetic organizations like CPIC (Clinical Pharmacogenetics Implementation Consortium – US) and DPWG (Dutch Pharmacogenomics Working Group - NL) provide guidelines and recommendations with clinical evidence of drug-gene interactions (53,57). In the Netherlands, the pharmacogenetic recommendations formulated by the DPWG - established by the ‘Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie’ (KNMP) – are incorporated in the national drug database (G-Standard) (10). All parties within the Dutch healthcare system can use it, for example, for the prescription of medicines.

Pharmacogenetics may be applied to several areas of medicine like cardiology, oncology and psychiatry (7). Several associations between drug response and genes – also called biomarkers – are recognized. Most drugs are metabolized by cytochrome P450 (CYP450) enzymes in the liver (31,32). About sixty CYP450 enzymes are known. The most important CYP450 enzymes for drug metabolism in humans are CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (5). Numerous genetic polymorphisms in these drug-metabolizing enzymes have been reported (5,26,33). Some drug-gene examples in this category are clopidogrel – CYP2C19, tamoxifen – CYP2D6, tacrolimus - CYP3A5 (5). Other genes that may play a role in the variation of the response to medicines are TMPT, UGT1A1, DPYD, VKORC1, HLA-B, NUDT15 and others (1,5). Some examples are irinotecan – UGT1A1, azathioprine – TMPT, simvastatin – SLCO1B1, warfarin – VKORC1, many beta-blockers – ADRB1, ADRB2 (1,5). It is expected that many more associations will be discovered (1).

Genetic testing can be used to determine for each liver enzyme in which phenotype category an individual fall into so that either the drug dose can be adjusted or an alternative treatment can be considered (5,8,53). Genetic variants or alleles can be detected with various

techniques (usually performed on blood cells) (58). An allele-specific polymerase chain reaction (PCR) can determine whether the DNA sequence of interest is present or not, using specific primer sets. Other techniques are becoming less expensive and thus more popular and are used to test more genes simultaneously: the best known technique is called next-generation sequencing NGS, (i.e. mapping a larger part of the genome). These novel techniques are expected to further contribute to constructing of a 'pharmacogenetic passport (PGx-Passport)'.

The Netherlands are amongst the leaders in the world in the application of pharmacogenetics (59). Pharmacogenetic tests can already be requested with an application form (e.g. by general practitioners) (60). Every individual can apply for a pharmacogenetic test or PGx-Passport (61) (see an example of a PGx-Passport in Fig.1). However, genetic testing is generally not used in daily routine care.

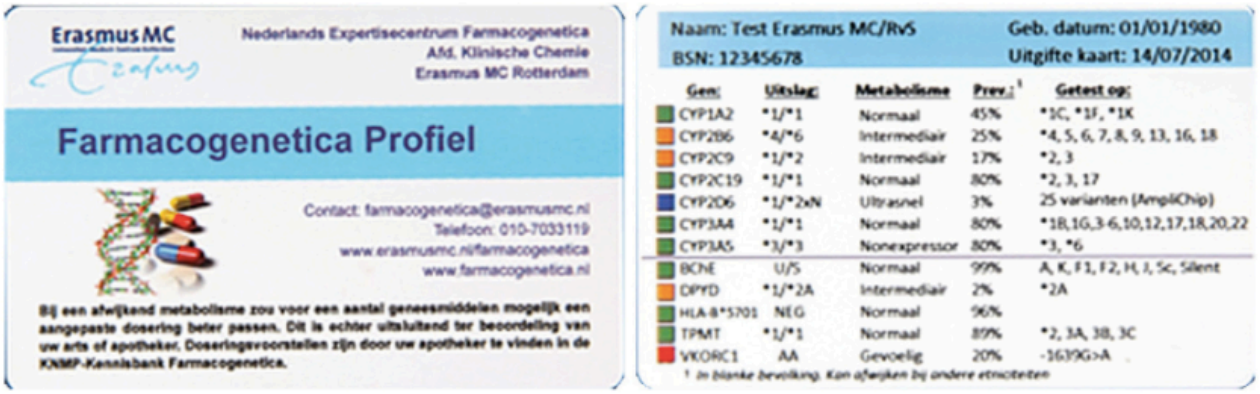


Figure 1: Example of a pharmacogenetic passport (Erasmus MC,2021)

2.2. Economic evaluation

Since healthcare resources are finite, it is essential to assess the cost-effectiveness of new pharmacogenetic-guided treatment strategies in addition to their clinical utility before their large-scale adoption in routine care (14). Economic evaluations "identify, measure, value and compare the benefits to the costs of the alternatives being considered." (62). If the genotyping-based treatment is cost-effective (more effective at acceptable additional costs or lower costs compared to the alternative), this is a well-considered reason for introducing the pharmacogenetic test in daily practice (14).

Good economic evaluations require several methodological choices (62,63). According to the Dutch and international guidelines (NICE for the UK (64), Zorginstituut Nederland (ZIN) for the Netherlands (65)), the following aspects should be addressed: audience, perspective, patient population, intervention, comparator, type of the economic evaluation, related health outcomes, time horizon, costs and effects, discounting rates, empirical/model-based approach, sensitivity analysis, supporting decision making.

Audience

The target audience of the economic evaluation should be specified (62). This can be ZIN for NL or NICE for UK, but also for example a health insurance company or health institution.

Perspective

The perspective determines which health benefits and costs are considered in an economic evaluation (62). Typical viewpoints are those of the patient, hospital/clinic, healthcare system, insurer, or the societal perspective. The societal perspective is the broader perspective that considers all costs and effects throughout society, regardless of who bears the costs or to whom the benefits accrue (62). NICE recommends a healthcare perspective (64), while the societal perspective is the standard for economic evaluations in the Netherlands (65).

Intervention

The intervention included in the study must be applicable and relevant in daily practice and should be clearly described (62,63). Information of the drug used, medical device, and diagnostic equipment are considered.

Patient population

The target population is the group for which the intervention is intended. Epidemiological data is used to define the patient population.

Comparator

It is important to choose the most appropriate comparator for the analysis. This could be do-nothing, placebo, standard care/care as usual, strategies varying by intensity or duration (62). Standard care is the most common comparator, but it might be country or health-system specific (65). The comparison of intervention strategy and comparator implies that the outcome is expressed in incremental or differential terms (62).

Time horizon

The time horizon is the period covered by the analysis and should be long enough the cover all the main costs and health effects (62). A lifetime horizon is often recommended and used (65), particularly when mortality is involved, but occasionally a shorter horizon may be appropriate depending on the problem at hand.

Type of economic evaluation

Type of economic evaluation refers to the economic evaluation framework: cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA). These types relate to costs in the same way but differ in terms of the measurement of health effects: health effects are equal or disregarded, expressed in monetary units, in health-related physical units, and in quality of life or QALYs, respectively (62). The outcome measures differ between the types of economic evaluation (see Related health outcomes below) (62).

Related health outcomes

Clinical outcome measures reflect morbidity, mortality or quality of life. Health-related quality of life is a description of the patient's health state, often reported by patients themselves (62). Quality-adjusted life-years (QALY) is a composite outcome measure that is regularly used linking life years and quality of life, and closely mirrors mortality and morbidity.

The related health outcomes depend on the target population, the specific condition of the disease and the purpose of the treatment. The outcome measures also differ between the types of economic evaluation (CMA, CBA, CEA, CUA): cost difference, the net monetary benefit or the cost/benefit ratio, costs per unit health effect (ICER), costs per QALY (ICER or ICUR), respectively (62). The incremental cost-effectiveness ratio (ICER) is defined as the ratio of the incremental costs divided by the incremental benefits of the new intervention compared to the standard of care (14,62).

The relevant effects should be identified, measured and in CUA and CBA valued (62). Utilities or valuations of patients' health states can be measured with various direct and indirect valuation techniques; e.g. time trade-off, standard gamble, contingent valuation or discrete choice experimentation. The questionnaire or valuation technique and the nationality of the respondents should be clearly indicated (62). The EQ-5D-5L questionnaire with Dutch valuation system ('tariffs') is the recommended method for economic evaluations in the Netherlands (65).

Costs

There are different cost types: direct medical (i.e., direct costs within health care), direct non-medical (i.e., direct costs outside health care such as patients and family costs and informal care costs), indirect medical (i.e., indirect costs within health care such as downstream costs: costs during life-years gained) and indirect non-medical costs (i.e., indirect costs outside health care such as productivity costs, judicial costs, special education) (62). Which cost types to include depends on the perspective used. The health care perspective includes only medical costs while the societal perspective is a broader perspective including all cost types (62). Important and relevant cost items should be identified. The resource use should then be measured accurately and in appropriate units, considering the chosen perspective and time

horizon, and valued. Each cost item is measured as the volume of (healthcare) resource use x (cost) price or reimbursement rate. Conversion (e.g. dollar to euro) and indexing (i.e., costs for different years are equalized using the general price index or a cost index) of costs should be applied when necessary (62).

Discounting effects and costs

Effects and costs should be discounted because individuals have a time preference. Discounting is the method of calculation by which costs and health effects of the intervention and the comparator that occur at different times can be compared (62). The method converts the value of future costs and health effects into their present value. This is done by dividing the costs or effects by the discount factor. NICE recommends using a discount rate of 3.5% for both costs and effects (64). In the Netherlands, the discount rates for the costs and effects are 4% and 1.5%, respectively (65)

Empirical/modelling approach

The empirical approach uses direct, own observations, but often no information on the full lifespan is provided in this approach, usually only on a relatively short follow-up period. A modelling approach is particularly useful to extrapolate the data over time to estimate the costs and effects over the lifetime horizon (62). The most common modelling techniques are: decision trees, "state-transition" models (also known as Markov models), "discrete event" simulations, and "dynamic transmission" models (65).

A Markov model (used in this thesis) consist of health states with transition pathways. It is assumed that all patients start in the start state and that for each cycle they can remain in the same state or change to another state. Those who die (disease-specific mortality, background mortality) can only remain in the death state (63). The cycle length should be determined by the expected frequency of clinical events and interventions. It is generally recommended to build a 'half-cycle correction' into the analysis, to account for the fact that events and transitions can occur at any point during the cycle (63).

The input parameters for the model are transition probabilities (between the states), costs (per state), effects and utilities (per state), often gathered from literature, empirical sources, or expert opinion (62). Assumptions often should be made because some data are missing or not fully relevant for the specific study (e.g. less relevant data from other countries is used when input data for the specific country is missing) (65). Also, in many cases, long-term population data may be missing (65). Economic evaluations for a longer time horizon can be performed by using statistical extrapolation techniques. To estimate the model probabilities, the observed probabilities (e.g. from Kaplan Meier curves) should be used to estimate the underlying individual patient data (IPD) as described by Hoyle & Henley (66). Parametric distributions (exponential, Weibull, lognormal, loglogistic) are often used to fit and extrapolate the observed data beyond the follow-up horizon. The choice for the parametric distribution should be justified.

Sensitivity analysis

The results of a model-based economic evaluation are surrounded by uncertainty (parameter uncertainty and structural uncertainty) because assumptions about the model and about the parameters are made (62,63). If the result is sensitive to changes in a specific parameter, this may guide areas for further investigation.

The influence of parameter uncertainty in the model-based economic evaluation should be considered using sensitivity analysis (62). A probabilistic sensitivity analysis (PSA) is conducted to explore uncertainty around the model parameters and to evaluate the model's robustness. The PSA must include all uncertain parameters. The distributions used must be reported and justified. The degree of variation in the distribution must also always be justified (65). Monte Carlo simulations should be carried out to estimate the average model results and the corresponding ICERs. Univariate (deterministic) sensitivity analysis should also be used to provide insight into the relative influence of input parameters on the ICER and the effects of fixed values in the model, such as discount rates and prices (65). How much (%) does the ICER vary when one parameter is varied (with a fixed %), holding the other parameters constant, is addressed in the univariate sensitivity analysis. Scenario analysis should be used to address structural uncertainty (62).

Supporting decision making and reporting results

Results from the base case should be reported: absolute costs and effects for the alternatives (also disaggregated costs and effects), the incremental costs and effects and the ICER (65). The ICER is compared to a societal willingness to pay (WTP) threshold to determine cost-effectiveness. The societal WTP threshold represents the amount of money that society is maximum willing to pay for incremental health gains (62). In the Netherlands, threshold values of €20,000 to €80,000 per QALY gained for a CUA are commonly used, depending on the severity of the disease (67). An ICER lower than the societal threshold ICER is thought to indicate that implementation, insurance coverage and reimbursement are societally preferable. The converse is true for an ICER that exceeds the societal threshold ICER. The incremental costs (y-axis) and incremental effects (x-axis) are represented in the four-quadrant cost-effectiveness plane (CE-plane). A theoretical CE-plane is presented in Fig.2 and shows the different situations in which an intervention is cost-effective.

The deterministic sensitivity analysis results, the minimum and maximum ICER for the parameters that are altered for the selected range and the incremental costs and effects of which these ICERs are composed, should be reported. It is recommended to visualize the ICERs for the parameters most affecting the ICER in a 'tornado diagram' (65). The incremental costs, incremental QALYs and resulting ICER associated with the scenario analysis must also be reported (65).

To capture the parameter uncertainty on the ICER, the results of the probabilistic sensitivity analysis are shown in the CE-plane (65). The ICERs resulting from the Monte Carlo simulations are often represented as a cloud of points in the CE-plane. The probability that alternative treatment is cost-effective compared to standard treatment at different thresholds is displayed in the cost-effectiveness acceptance curve (CEAC) (65). The CEAC gives an overview of the probability that the intervention is cost-effective for different thresholds of willingness to pay. The graphical representation is derived from the CE-plane by plotting the percentage of simulations (i.e. ICERs) that are cost-effective for varying threshold values (63). The impact of uncertainties shall be clearly described.

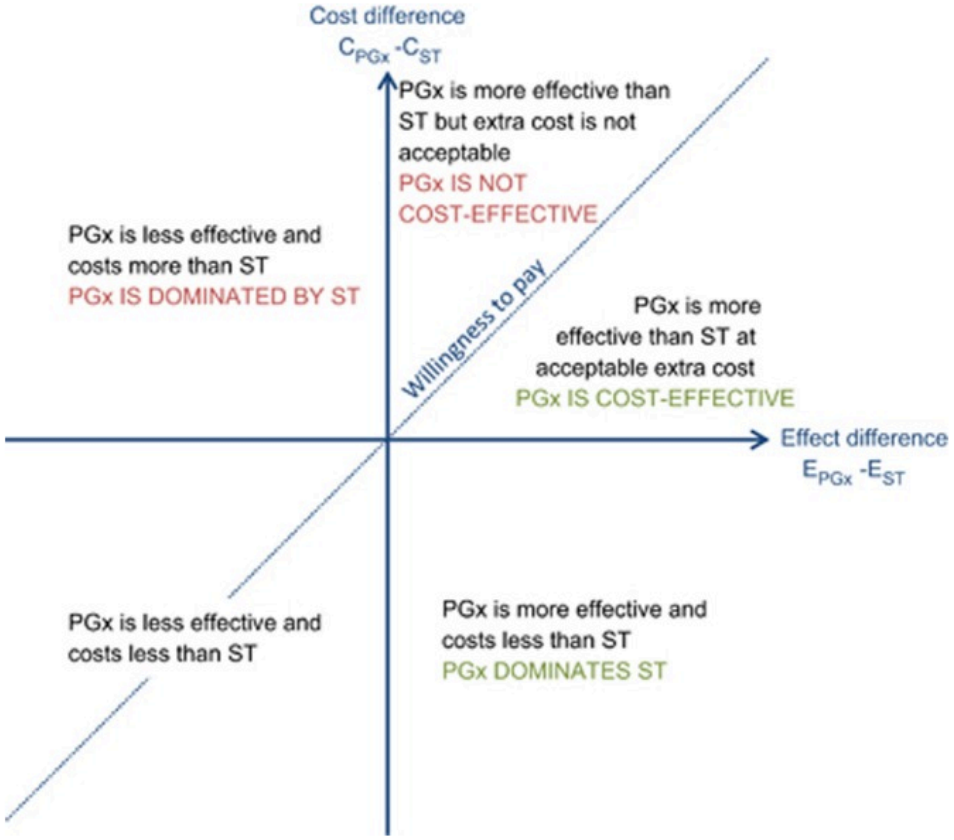


Figure 2: Theoretical CE-plane for PGx treatments (Verbelen et al. 2017)

3. Methodology

3.1. Overview

Cost-utility analysis is performed to evaluate the effectiveness of tamoxifen treatment based on genotyping for the CYP2D6-enzyme. The treatment strategies are shown in Fig.3. Based on the individual's genetic profile, women without a CYP2D6 'slow metabolizer' polymorphism receive the standard dose of tamoxifen (20mg/day) for five years, while women with a CYP2D6 'slow metabolizer' polymorphism receive a twofold increased dose of tamoxifen (40mg/day) for five years. The genotyping-based (PGx) strategy is compared with the current standard of care (SOC strategy) in the Netherlands for patients prescribed monotherapy tamoxifen: tamoxifen at a dose of 20mg/day for five years.

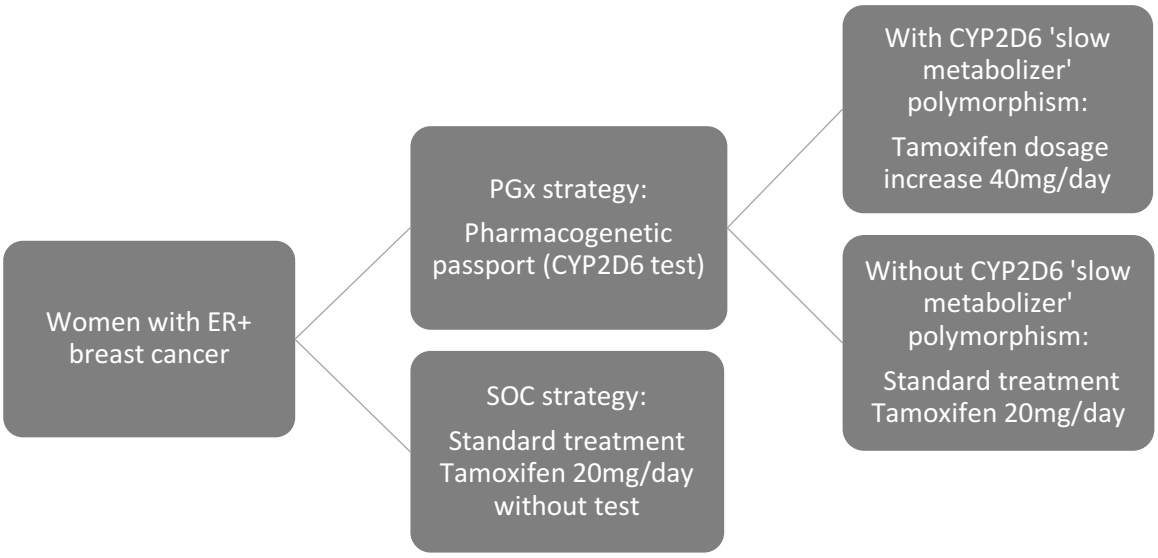


Figure 3: Decision tree PGx strategy and standard of care strategy

A Cohort Markov model is used to analyze the costs and effects of the two alternative strategies in a hypothetical cohort of 50 year-old-women with ER+ early breast cancer treated with tamoxifen. This type of model is also suitable for considering the ongoing risk of disease progression and death of patients, which is essential in the disease process of breast cancer. Since the follow-up of the survival estimates reported in the clinical trials (23,38) is insufficiently long to cover the lifetime horizon – as recommended by ZIN - a model is needed to extrapolate the data beyond the empirical time horizon. The Markov model consists of health states that represent the progression of breast cancer. During each cycle, patients can stay in a health state or move to a different health state with transition probabilities. Costs and effects are attributed to each of the health states.

The relevant health outcomes for each strategy in our model are relapse/recurrence outcome such as disease-free survival (DFS), life-years gained (LYs) and quality-adjusted life-years (QALYs). Treatment impacts prognosis and health-related quality of life, which necessitates the use of the composite outcomes measure of QALYs. Appropriate (dis)utility values for the health states and the tamoxifen related adverse events are used to quantify the health-related quality of life. By considering the additional (QA)LYs versus the additional costs between the strategies, the cost-effectiveness can be expressed in incremental cost-effectiveness ratios (ICERs) – 'cost per (QA)LY gained'.

The aim is to carry out the cost-utility analysis from the Dutch social perspective. Both medical costs (cost of hormone therapy, treatment of adverse events, diagnosis of recurrences, treatment of recurrences, follow-up, pharmacogenetic testing, palliative care) and non-medical costs (transport costs and costs due to productivity loss) are included in the analysis. All cost estimates are adjusted to the baseline year 2020 using the Dutch consumer price indexes (68). Costs and effects are discounted with a 4% and 1.5% discount rate, respectively (see section 3.5.4). The model is implemented in Excel - using the template used in the AHEM course, Erasmus University - to obtain the results.

3.2. Model structure

Markov model structure is shown in Fig.4. Tamoxifen is the standard adjuvant hormone treatment for women with ER+ early breast cancer (6). Patients are assumed to start in the stable disease health state without adverse events. Patients are thus considered to have successfully completed the primary therapy. The disease-free patients are at risk of breast cancer recurrences, either local recurrence (including contralateral breast cancer and regional recurrence) or distant metastases. Patients with a local recurrence may also develop metastases. Disease-free patients are treated with tamoxifen (see Fig.3), which increases the risk of endometrial cancer, fractures, thromboembolic events, cerebrovascular events, cardiovascular events, vaginal bleeding and hot flushes (27). The most severe adverse events, i.e. thromboembolic events and endometrial cancer, are included in the model. Recurrences are treated again with a series of procedures - including treatment with tamoxifen if necessary. It is assumed that breast cancer-specific death always occurs after metastasis, in agreement with clinical practice (69). Mortality from causes other than breast cancer (background mortality) is also considered in the model.

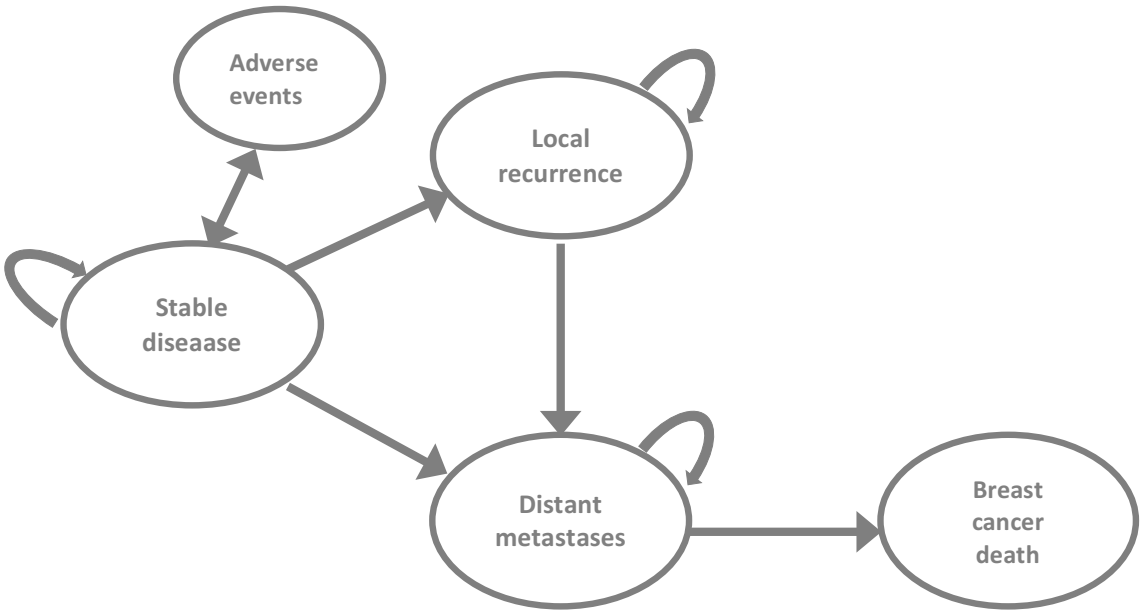


Figure 4: Markov model structure

The length of the cycle is set at one year to record clinical events and the application of interventions adequately. A 'half-cycle correction' is applied to multiple cost and effect categories to account for events and transitions occurring at any point in a cycle (see section 3.5.4.). As the adverse events are specified over the entire time horizon in the studies used, the frequency, costs and disutility associated with the adverse events are considered a one-off, rather than per cycle and per cohort.

3.3. Patient group

The target population are women with ER+ early breast cancer – with or without the CYP2D6 'slow metabolizer' polymorphism - who have successfully completed the primary therapy and have been prescribed tamoxifen for five years as adjuvant therapy. In the Netherlands, this group includes postmenopausal women with a contraindication for aromatase inhibitors and premenopausal women (22). Based on pharmacogenetic information, this is the target group for increasing the tamoxifen dose if they have a CYP2D6 'slow metabolizer' polymorphism (44).

The characteristics of the patients included in the hypothetical cohort are based on the patient characteristics of the EBCTCG clinical study (23).

- Patients diagnosed with early oestrogen receptor-positive (ER+) breast cancer
- Patients who have completed breast cancer surgery and chemotherapy when needed
- Patients initiated with tamoxifen as standard adjuvant therapy for five years
- Average age of patients at entry 50 years.

Patients in this study are categorized as a CYP2D6 'slow metabolizer' if they genotype for at least one intermediate or one non-functional allele, as in the study by Schroth et al. (38). Included CYP2D6 variants are 2D6*3, 2D6*4, 2D6*5, 2D6*10, 2D6*41. CYP2D6*4 variants are the main variants in the study by Schroth and in the Dutch population, around 18% of the population (26,34).

3.4. Data collection method

The treatment protocols are based on the Dutch breast cancer guideline (21). The cost-utility analysis is based on the Dutch guideline for economic evaluation in healthcare (Zorginstituut Nederland – ZIN (65)). The input parameters for the Markov model - transition probabilities, costs and utilities – are gathered from literature and external resources. The aim is to collect Dutch specific parameters. When unavailable, international data is used instead. Assumptions are formulated when necessary.

Data on survival estimates are obtained from relevant clinical studies. The 'Cost Manual' (70) provided by ZIN is preferably used for standard cost prices. As recommended by ZIN, utilities should be measured with the EQ-5D-5L with Dutch valuation (65).

3.5. Input parameters

3.5.1. Transition probabilities

The transition probabilities are estimated to calculate the number of patients in each health state in each cycle for the PGx strategy and SOC strategy.

Two clinical studies are observed to obtain survival estimates of breast cancer recurrence and breast cancer mortality (23,38). The meta-analysis from the international EBCTCG (Early Breast Cancer Trialists' Collaborative Group) (23) investigates the efficacy of 5 years of tamoxifen during 15 years for all ER+ breast cancer patients. Schroth et al. (38) examine the effectiveness of 5 years of tamoxifen during 15 years in early ER+ breast cancer patients comparing the different CYP2D6 genotypes (Germany and US). The EBCTCG trial reports a substantial reduction in the recurrence rates and breast cancer mortality rates - about a third throughout the first 15 years - compared to no tamoxifen treatment (23). Schroth et al. report a significantly reduced risk of recurrence for patients without a CYP2D6 'slow metabolizer' polymorphism (normal metabolizers) compared to those patients with a CYP2D6 'slow metabolizer' polymorphism (slow metabolizers) (hazard ratio 1.29) (38).

Despite a different average starting age in both studies (study by EBCTCG (23): 50 yrs vs study by Schroth et al. (38): 66 yrs), the presented recurrence probability curve for patients, independent of their genetic information, is similar. Schroth et al. report the recurrence rates un-stratified patients and the CYP2D6 genotypes (38). Therefore, the Kaplan-Meier (KM) recurrence curves presented by Schroth et al. (38) are used to estimate the transition probabilities in both strategies. Increasing the tamoxifen dose by a factor of 1.5-2 for slow metabolizers leads to comparable, non-significant recurrence rates as patients without a CYP2D6 'slow metabolizer' polymorphism receiving the standard dose (45-48). This means that the data for the patients without CYP2D6 'slow metabolizer' polymorphism - presented by Schroth et al. (38) – apply to all patients in the genotyping-based strategy. The recurrence probability curves are fit and extrapolated to the lifetime horizon along four distinct parametric distributions (exponential, Weibull, lognormal and log-logistic) using a maximum likelihood method (66). The AIC, intercept and log(scale) parameter values for the distributions are obtained by R software. KM and parametric distributions for recurrence probabilities are presented in Appendix 1. In both strategies, the extrapolated curves are below the observed curves, resulting in an overestimation of the breast cancer recurrences.

Based on the best fit per Akaike Information Criterion (AIC) and clinical plausibility, the exponential distribution (SOC: AIC = 2072.052 standard of care: $\lambda = 0.0022$; PGx: AIC=781.849 $\lambda = 0.0018$) was selected to model recurrence probabilities for both strategies.

The breast cancer mortality rates for the different genotypes are not significantly different (38) and are therefore assumed to be the same for both strategies. The breast cancer mortality curve is obtained from the EBCTCG study (23) as no curve is provided by Schroth et al. (38) (Appendix 2). The extrapolation of the curve, as described by Hoyle & Henley (66), was not successful, so it was decided to extrapolate the curve manually. Taking 70% of the recurrence rates for the SOC strategy seems to approximate the observed part of the mortality curve (38), and this fraction was used to extrapolate the curve manually. The total mortality is obtained by adding the breast cancer mortality to the age-specific background mortality for women in the Netherlands, according to the data from Statistics Netherlands (71). The overall mortality probability is assumed to take value one if the sum of background mortality and breast cancer mortality exceeds one.

The overall survival estimates are thus expected to be the same in both treatment strategies. In contrast, the disease-free survival estimates are higher in the PGx strategy than the SOC strategy.

The probability that a recurrence is a local recurrence or distant metastasis and the probability that patients with a local recurrence develop metastasis is taken from Geurts et al. (72) based on Dutch breast cancer patients. These probabilities are expected to be constant over time as indicated by Geurts et al. (72) (see Table 1).

Table 1: Constant probabilities between recurrence stages

Health states	Value	Standard error[a]	Source
Probability that recurrences are local recurrences (%local)	27.50%	5.50%	(72)
Probability that recurrences are distant metastases (%metastases)	72.50%	14.50%	(72)
Probability of patients with local recurrences developing metastases (%local_metastases)	28.00%	5.60%	(72)
Source: Geurts et al., 2017			

[a] SE based on 20% of the mean

3.5.2. Health-related quality of life

Health states

Data on the valuations of health-related quality of life (HRQL) for the various health states, i.e. utility values, are collected from a previous Dutch cost-effectiveness analysis (73). The study obtained the quality of life weights from a cross-sectional survey among patients with breast cancer in medical centers in the Netherlands (n=268), using the EQ-5D questionnaire (5L or 3L not reported). The utility values for stable disease and recurrent disease health states are summarized in Table 2. Different utility values are observed in the first year after entering the health state and the years after the first year. For simplicity, an average utility score for local and distant recurrences is used. The same values are assumed in the genotyping-based treatment arm.

Table 2: Health state utilities

Health states	Utility value	Standard error[a]
Stable disease		
Year 1	0.728	0.016
Years 1+	0.805	0.021
Recurrent disease - local recurrence		
Average	0.717	0.055
Recurrent disease - distant metastases		
Average	0.594	0.055

Source: (73)

[a] SE based on source (73)

Adverse events

Literature suggests that a dose increase of tamoxifen does not affect the risk of adverse effects (AE) (45). Therefore, the parameters for the AEs are expected to be similar in both treatment strategies (SOC and PGx strategy). The incidence rate for endometrial cancer for women receiving tamoxifen is taken from Integraal Kankercentrum Nederland (74). The incidence rate for thromboembolic events for women receiving tamoxifen is based on the average incidences reported in international studies (27, 29). Duration data are based on the international study by Skedgel et al. (75). The utility values for the AEs are taken from Dutch literature measured with the EQ-5D-3L questionnaire. Utility scores for thromboembolic events and endometrial cancer of Dutch individuals are derived from Locadia et al. (76) and Korfage et al. (77), respectively. The disutilities (i.e. utility decrement) for the AEs are

calculated by 1 (full health) minus the utility values of the AEs, as these utility values apply to healthy individuals. Details are provided in Table 3.

Table 3: Adverse events disutilities

Adverse events	**Incidence (SE)**	**Duration (SE[a]) (years)**	**Utility (SE[b])**	**Disutility**
Thromboembolic events	2.5% (0.50%)	0.5	0.7730 (0.0773)	0.227
Endometrial cancer	1.2% (0.24%)	5	0.8140 (0.0814)	0.186
Source	(27,29) (74)	(75)	(76) (77)	
AE disutility per cycle (corrected for duration and incidence)				0.0140

[a] SE based on 10% of the mean
[b] SE based on 10% of the mean

The information on utility values for the health states and AEs is used to calculate the total quality-adjusted life-years (QALYs) for the treatment strategies. The total QALYs are calculated using the QALYs obtained in the stable disease health state, recurrent disease health states, and the QALYs lost due to the AEs.

The calculated life years accumulated in the stable disease state and life years accumulated in recurrent disease states are multiplied by the state-specific utility values (variable utility values for stable disease between the first year of entering a state and afterwards; see Table 2) to obtain the QALYs in the health states. These values are discounted using a discount rate of 1.5% as prescribed by ZIN for outcomes and then half-cycle corrected.

To measure the total QALYs lost due to AEs, duration (in years) and incidence rates are taken into account to calculate the individual AE disutility for tamoxifen. All AE disutilities are then added together to calculate the total AE disutility per treatment. The QALYs lost due to AE are applied once at the beginning of the first cycle, as data per cycle are lacking. The disutilities are multiplied by the number of patients starting in the stable disease state at t=0 to obtain the total QALYs lost due to AEs.

3.5.3. Costs

The costs of the PGX and SOC treatment strategies are considered equal, except that the costs of intensified tamoxifen treatment and CYP2D6-enzyme testing are also added to the PGx strategy. The different cost categories are explained below. The average costs per cycle per patient for the different cost categories are shown in Appendix 3, according to the Dutch guideline for breast cancer (21) for the different components.

3.5.3.1. Medical costs

Stable disease costs

The medical costs of the stable disease include: costs of tamoxifen treatment, costs of annual follow-up, and cost for treating the adverse events. The costs of genotyping CYP2D6 are only included in the PGx strategy.

Costs of genotyping

The costs of CYP2D6 genotyping screening is based on Erasmus MC (78) (targeted testing), presented in Table 4.

Table 4: Cost CYP2D6 testing

Genotyping CYP2D6	Value (SE[a])	Source
CYP2D6 testing	€184.50 (€36.40)	(78)

[a] SE based on 20% of the mean

The costs associated with genotyping the CYP2D6-enzyme are multiplied by all the patients entering the model for the PGx strategy. The costs are allocated at the start of the first cycle.

Costs of tamoxifen

Tamoxifen is given for a maximum duration of 5 cycles for disease-free patients. It is assumed that tamoxifen treatment is stopped when a recurrence is detected. The unit prices are taken from the official site of the ZIN for information on medicine prices; Medicijnenkosten.nl (79). Other parameters such as the dose of tamoxifen and the frequency are derived from the Dutch guideline for breast cancer (22). The incidence of CYP2D6 'slow metabolizer'

polymorphism in the Dutch population is based on KNMP (34): thus, 20% of the patients receive the higher tamoxifen dose in the PGx strategy. Details are presented in Table 5.

Table 5: Costs tamoxifen treatment

Hormonal therapy	Value	Source
Tamoxifen (Sandoz 20mg)		
Unit price tablet	€0.25	(79)
Dosage	20 mg/day	(22)
Frequency per cycle (year)	365	(22)
Tamoxifen (Sandoz 40mg)		
Unit price tablet	€0.40	(79)
Dosage	40 mg/day	(22)
Frequency per cycle (year)	365	(22)
Incidence CYP2D6 'slow metabolizer' polymorphism	20%	(34)

The average tamoxifen acquisition cost per cycle in the standard of care strategy is calculated by multiplying the unit price per tablet (20mg/day) by the frequency per year. The cost per cycle in the PGx strategy is calculated by multiplying the unit price per tablet (20mg/day) by the frequency per year for the proportion of patients without CYP2D6 'slow metabolizer' polymorphism plus multiplying the unit price per tablet (40mg/day) by the frequency per year for the proportion of patients with CYP2D6 'slow metabolizer' polymorphism.

The cost per treatment cycle is multiplied by the number of patients in the cohort with stable disease for the first five cycles of the Markov trace. The acquisition cost of tamoxifen is counted once at the start of the treatment cycle.

Follow up

The patients are monitored annually to detect any recurrence. The Dutch guideline for breast cancer recommends an annual follow-up consisting of a clinical examination and a mammography (21). In the first five years after diagnosis/last mammography before surgery, the clinical examination is carried out by the clinical oncologist in the hospital and the following years by the general practitioner (21). It is assumed that follow-up occurs during the remainder of the patient's life.

The unit costs for the follow-up care are derived from the Dutch cost manual (70) and the Dutch price list for primary diagnostics (unit cost includes costs and honorary fees) (80). Details are shown in Table 6.

Table 6: Costs follow-up care

Follow-up care	Use per cycle	Cost (SE[a])	Source
Mammography	1	€90.88 (€18.18)	(80)
Visit to clinical oncologist (clinical examination)	1	€98.41 (€19.68)	(70)
Visit to GP (clinical examination)	1	€35.69 (€7.14)	(70)

[a] SE based on 20% of the mean

The costs related to the annual follow-up are calculated by adding up the unit costs of the relevant components of the annual follow-up.

The cost per cycle is multiplied by the number of patients in the cohort with stable disease. In the first five cycles, disease-free patients receive annual follow-up with the clinical examination by the oncologist. In the following years, they receive annual follow-up with the clinical examination by the general practitioner. The follow-up occurs across the cycle, so half-cycle correction is needed. It is assumed that the annual follow-up applies to the remainder of a patient's life.

Adverse events

The costs associated with treatment of adverse events (AEs) are collected from published Dutch cost-effectiveness studies (see Table 7). Thromboembolic events include stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism (81). The treatment costs for these events vary widely (81,82). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are most common in cancer patients treated with tamoxifen (27,29). The cost of treating PE is assumed to be the average cost of treating a thromboembolic event - higher costs than DVT, but significantly lower than other, less common thromboembolic events - and is taken from the Dutch study by Ten Cate-Hoek et al. (82). The cost of endometrial cancer treatment is derived from Van Ballegooijen M. (83). Detailed information on the specific cost components in the treatment of the AEs is shown in Appendix 4 and 5.

Table 7: Costs adverse events

Adverse events	Costs (SE[a])	Source
Thromboembolic events	€5,425 (1,085)	(82)
Endometrial cancer	€38,118 (7,624)	(83)

[a] SE based on 20% of the mean

The incidences of the AEs are taken into account to calculate the costs related to the AEs. AEs costs are counted as a one-off for all patients in stable disease at the start of the first cycle, as no incidence data are given per cycle. AEs related to the recurrences are included in the treatment of recurrences (see section Treatment of recurrences).

Recurrent disease costs

Local and distant recurrences involve medical costs associated with the diagnosis and treatment of the recurrence and the annual follow-up.

Diagnostics

Local recurrences are usually discovered during the annual follow up. During this follow-up, patients with suspicious features are further examined to locate the cancer and determine the treatment strategy (21). A fixed set of examinations/tests is assumed to diagnose local recurrences based on the Dutch breast cancer guideline (21): histological biopsy (to obtain the tumor characteristics), breast ultrasound and breast MRI.

Metastases are usually detected based on the patient's complaints. The location and the extent of the metastasis must be determined, which influences the choice of therapy. The most common metastases in breast cancer are metastases to the skeleton, metastases to the lungs, pleura, mediastinum and airways, metastases to the liver and metastases to the brain. A fixed set of imaging techniques is assumed to locate the metastases, based on the Dutch breast cancer guideline (21):

- Bone scan (skeletal metastases)
- Chest X-ray (lung metastases)
- Ultrasound abdomen (liver metastases)
- CT scan breast (liver metastases)
- CT scan abdomen (chest metastases)
- MRI cerebrum (brain metastases)

Histological analysis is supposed to follow to confirm and characterize the metastatic tumor.

The unit costs of the imaging tests are derived from the Dutch price list for primary diagnostics (unit cost = costs and honorary fee) (80). If a diagnostic test is not included in the list, the unit cost is taken from a Dutch study by Laarakker&Nek (84). The unit cost of the histological analysis is taken from the Dutch study by Timmers et al. (85). Values for the diagnosis of local recurrences are shown in Table 8 and for distant metastases in Table 9.

Table 8: Costs diagnosis local recurrence

Diagnostics – local recurrence	**Cost (SE[a])**	**Source**
Histological analysis	€187.51 (€37.50)	(85)
Ultrasound mamma	€82.54 (€16.51)	(80)
MRI breast	€235.41 (€47.08)	(80)

[a] SE based on 20% of the mean

Table 9: Costs diagnosis metastases

Diagnostics – distant metastases	**Cost (SE[a])**	**Source**
Bone scan	€215.00 (€43.00)	(84)
Ultrasound abdomen	€108.44 (€21.69)	(80)
Chest X-ray	€56.89 (€11.38)	(80)
CT scan breast	€215.00 (€43.00)	(84)
CT scan abdomen	€235.41 (€47.08)	(80)
MRI cerebrum	€274.84 (€54.99)	(80)
Histological analysis	€187.51 (€37.50)	(85)

[a] SE based on 20% of the mean

The cost of diagnostics for recurrences is obtained by adding up the unit costs of the associated examinations/tests.

The average costs per new patient with a recurrence are multiplied by the number of new patients entering the specific recurrence stage in each cycle of the Markov trace. The number of new relapsed patients for each cycle can be approximated by subtracting the number of patients in recurrent disease (+breast cancer death) in the previous cycle from the number of patients in recurrent disease (+breast cancer death) in a given model cycle, taking into account the percentage that recurrences are local or metastases. Patients with local recurrences are also at risk of developing metastases, so they are also counted among the new patients who develop metastases at the time they reach the 'distant metastases' stage. It is assumed that the cost of the diagnosis occurs only once at the beginning of the first year of entering a recurrence health state.

Treatment of recurrence

In general, local treatment is chosen with a curative aim, whereas metastatic breast cancer is considered an incurable disease (21). Depending on the patient's characteristics, the tumor (size and extent), primary treatment and the interval between primary treatment and recurrence, a range of procedures are performed to treat the recurrence (21).

The same set of procedures as in the Belgian study by Cocquyt et al. (86) are assumed for treating recurrences in the Netherlands. The range of procedures is the same for local recurrences and metastases but with different volumes. In the Belgian study, the average frequencies per patient of the procedures are not reported, except for the precise number of hospital days, the number of days in a day clinic and the number of visits during the treatment period of recurrences. The current study assumes the same frequencies for these components but uses the unit costs from the Dutch literature to calculate the average cost per patient for these procedures over the treatment period (87). Detailed information for these parameters can be found in Appendix 6. The average costs per patient for the other components - the frequencies of which are not exactly known - have been taken from the Belgian study (86). The average costs per patient for the procedures are shown in table 10.

Table 10: Costs of treatment of recurrences

	Breast cancer treatment costs (€)		
Treatment	Local recurrence	Distant metastases	Source
	Cost (SE[b])	Cost (SE[b])	
Surgery	€433.40 (€109.65)	€ 537.83 (€97.91)	(86)
Radiotherapy	€1,029.97 (€262.39)	€ 858.96 (€242.81)	(86)
Chemotherapy	€7,959.11 (€3,439.77)	€ 6,566.24 (€1,002.56)	(86)
Endocrine	€390.32 (€124.01)	€ 379.88 (€86.16)	(86)
Other treatment	€250.64 (€191.90)	€ 298.94 (€114.88)	(86)
Other drugs	€382.49 (€150.12)	€ 2,627.80 (€1,194.45)	(86)
Imaging	€753.22 (€241.50)	€ 1,985.54 (€172.31)	(86)
Pathology	€134.46 (€39.16)	€ 117.49 (€28.72)	(86)
Markers	€53.52 (€15.66)	€ 100.52 (€9.14)	(86)
Other tests	€417.73 (€140.88)	€ 481.70 (€90.07)	(86)
Visits[a,c]	€5,158.09	€ 8,468.13	(86,87)
Day clinic[c]	€2,155.07	€ 2,575.93	(70,86,87)
Hospital[c]	€1,109.91	€ 1,784.43	(70,86,87)

[a] Visits include oncological visits in hospital and ambulatory visits and honorary fees and nursing care.
[b] SE based in source (86)
[c] Components are explained in detail in Appendix X with unit costs, frequencies and SE.

The average cost per patient for the treatment of a recurrence is calculated by adding up the costs of the various components. These average treatment costs per new patient with a recurrence are incorporated in the model in the same way as the diagnosis costs.

Follow up

The follow-up period begins after a 3-month treatment period and is then conducted annually (21). It is assumed that patients with the recurrent disease receive the same annual follow-up as patients in the stable health state (see Table 6 for the unit costs).

The cost per cycle is multiplied by the number of patients in each cycle with the recurrence. The follow-up occurs across the cycle, so half-cycle correction is needed. Follow-up applies to the rest of a patient's life.

Breast cancer death costs

End of life costs

The end-of-life costs are attributed to the new patients entering the breast cancer death state $(Breast\ cancer\ death_{t-1} - Breast\ cancer\ death_t)$ and assume three months of palliative care (21). The costs were taken from the Dutch study by Schneider et al. (88), in which costs were calculated based on Dutch patients with advanced breast cancer who were diagnosed between 2010 and 2017 and who died during that period. Most costs are associated with hospitalization costs. The average end of life costs for a patient entering the death state per cycle is shown in Table 11. Detailed information on the cost elements belonging to these end-of-life costs can be found in Appendix 7. It is assumed that the costs occur across the cycle, so they need to be half-cycle corrected.

Table 11: Costs end of life

End of life costs	Value (SE[a])	Source
Palliative care	€9,301.66 (€1,860.33)	(88)

[a] SE based on 20% of the mean

3.5.3.2. Non-medical costs

Transport costs and costs due to productivity loss occur in each of the health states but in different amounts. The costs are associated with the medical cost categories (follow up, diagnosis and treatment of recurrences and palliative care) as they require travel and time. The average frequencies per patient of visits (to GP or hospital), day clinic (in days) and hospital stay (in days) per cost category are required to determine the costs due to productivity loss and due to transport. Two visits are assumed for the annual follow up. Three visits are assumed for diagnosing the recurrences. The frequencies for the treatment of recurrences are derived from the Belgian study Cocquyt et al. (86) and are shown in Appendix 8.

The transport costs and the costs due to productivity loss (detailed information below) are implemented in the model the same way as the associated cost categories. The costs related to productivity loss are only considered up to the average retirement age in the Netherlands, i.e. 67 years old. This means up to cycle 17 in our model.

Transport costs

The average distances of a household to care organizations and the costs per kilometer per means of transport are taken from the Dutch Cost Manual (70). Parking costs are also taken into account for car journeys, with a distinction being made between average parking cost for a visit (independent of the care institution and duration) (70) and average parking cost for a day in the hospital (89). The proportion of patients who travel to healthcare facilities by car and by public transport is assumed to be 80% and 20% respectively (Taxi transport is not considered). For the possible trips - visit, day clinic, hospital stay - a return trip is always required: two trips on the same day for a visit and day clinic admission and two trips spread over three days for a hospital stay (average length of hospital stay is assumed to be three days). For simplicity, travel costs for a visit during treatment and follow-up are based on a visit to the general practitioner. Travel costs for diagnoses are based on a visit to the hospital. The input parameters are shown in Appendix 9.

The average transport costs are determined for the various trips, presented in Table 12. These are then multiplied with the frequencies corresponding to the different cost categories for each health state. No transport costs are charged for patients receiving palliative care (transport costs for persons other than the patient are not included in the model).

Table 12: Costs due to transport

Transport costs	**Value**[a]
Average transport cost of an average hospital stay (three days)	€24.40
Average transport cost for one admission to day clinic	€9.83
Average transport cost for a visit (hospital)	€5.18
Average transport cost for a visit (GP)	€3

[a] SE are formulated for the components, see Appendix 9

Productivity loss

Costs due to productivity losses (related to the absence of work) are included in the model using the friction method for valuing these losses, as recommended by ZIN (70). The friction period, productivity cost per hour per woman and the working hours per day are derived from the Dutch Cost Manual (70). It is assumed that each visit results in 1/4 of a day absence. These input parameters are shown in Appendix 10.

The average costs due to productivity loss are calculated for one visit, day clinic (per day) and hospital stay (per day), shown in Table 13. These are then multiplied with the frequencies corresponding to the different cost categories for each health state. Moreover, it is assumed that people are absent from work for the last three months before their death (palliative care).

Table 13: Costs due to productivity loss

Productivity loss	**Value**[a]
Costs due to productivity loss hospital stay (per day)	€273.40
Costs due to productivity loss day clinic (per day)	€273.40
Costs due to productivity loss visit (per visit)	€68.35

[a] SE are formulated for the components, see Appendix 10

3.5.4. Half cycle correction, discounting, indexing

Half-cycle correction (HCC)

A 'half-cycle correction' is applied to multiple cost and effect categories to account for events and transitions occurring at any point in a cycle (65).

$$X_{t+1\,HCC} = \frac{X_t + X_{t+1}}{2}$$

Where X_t and X_{t+1} are the components between two consecutive years that needed to be half-cycle corrected

Discounting

Costs that will be spent in the future need to be discounted to account for time preference. As required by ZIN, the discount rate is set at 1.5% for health effect and 4% for costs (65).

$$D_n = \frac{1}{(1+r)^n}$$

Where D_n = discount factor
r = discount rate
n = number of years ahead

Indexing

Some cost inputs were taken from documents and literature dating several years back. These values were indexed to account for inflation using the consumer price indexes (CPI) by CBS (68). Details are presented in Appendix 11. All costs are set at year 2020.

$$New\ cost_t = Old\ cost_{t-x} * (1 + \frac{CPI_{t-x}}{100}) * (1 + \frac{CPI_{t-x+1}}{100}) * (1 + \frac{CPI_{t-x+2}}{100}) \ldots * (1 + \frac{CPI_t}{100})$$

3.6. Sensitivity analysis

Scenario analysis

Selecting parametric curves to fit recurrence probability Kaplan-Meier curves from Schroth et al. (38) was done by assessing AIC values, a visual check and clinical plausibility of the curve. These criteria introduce considerable uncertainty into the model. The first part of the sensitivity analysis compares the ICER based on the other distributions: Weibull, lognormal and log-logistic.

Deterministic sensitivity analysis – one-way sensitivity analysis

Key model probabilities and costs are changed within a certain range around to base case values – based on parameter's degree of uncertainty and complexity: 20% for costs and probabilities, 10% for utilities - to determine the impact on the ICER: constant transition probabilities, CYP2D6 'slow metabolizer' polymorphism incidence, the cost of CYP2D6 testing, cost of tamoxifen, diagnostic cost of recurrences, treatment costs of recurrences, costs due to productivity losses, transport costs, utility health states. The results were also obtained using other discount rates for costs (7%, 1.5%) and effects (3%, 0.5%) and for patients starting tamoxifen at the ages of 40 and 60. The results will be presented in a table as well as in a tornado diagram.

Probabilistic sensitivity analysis

First, uncertainty among the recurrence probability curve is implemented by multiplying the intercept and log(scale) values with randomly generated values taken from a normal distribution. Additionally, parameters considered uncertain are varied simultaneously. When standard errors are available from the source, these are applied accordingly. If unavailable, a percentage of the mean is taken, varying between 5%, 10%, and 20%, based on the parameter's degree of uncertainty and complexity. In general, 10% is assumed for utilities and 20% for costs, resource use and probability parameters. Standard errors (SE) are included in the cost and effect tables. The method of obtaining the SE is specified in the table description.

A beta distribution is used for probabilities and utilities, as these values are restricted between 0 and 1. All other parameters, including costs and resource uses, are varied in a gamma distribution, as these values can only take on positive values. Respective alpha and beta parameters are calculated in a standard manner.

All parameters that are considered uncertain are varied randomly and simultaneously using the assigned distributions. 1000 simulations have been run to estimate the mean model results (costs, LYs, QALYs) and the corresponding ICERs. Results of the analyses are presented in a cost-effectiveness plane (CE-plane). A cost-effectiveness acceptability curve (CEAC) is also constructed by identifying the proportion of simulations for which the PGx strategy was preferred at different levels of willingness to pay for a QALY. A societal WTP of €20,000 is assumed for the genotyping-based strategy for adjuvant tamoxifen treatment compared to the standard of care.

3.7. Validity and reliability

Deterministic and probabilistic sensitivity analysis will be used to assess the reliability of the ICER. Internal validation (i.e. the extent to which the results of a study accurately represent the causal relationship between an intervention and an outcome in the circumstances of that study) and external validation (i.e. the extent to which the results of a study conducted under circumstances can be generalized to other patients, populations, or other) will also be addressed, particularly the validity of the Markov model and the validity of the input data. AdViSHE and TECHVER are validation specific tools that will be performed during and after modelling (90,91).

4. Results

4.1. Base case results

Disaggregated costs & effects

Table 14: Disaggregated costs and effects (base case) after discounting

	Treatment	PGx strategy	Standard of care strategy	Increment (PGx-SOC)
Stable disease	CYP2D6 testing	€ 185	€ 0	€ 185
	Tamoxifen acquisition costs	€ 572	€ 504	€ 68
	Follow-up costs	€ 2,794	€ 2,561	€ 233
	Transport costs	€ 117	€ 107	€ 10
	Costs due to productivity loss	€ 1,851	€ 1,770	€ 81
	AE costs	€ 593	€ 593	€ 0
Recurrent disease – local recurrence	Diagnostic costs	€ 74	€ 85	-€ 11
	Treatment costs	€ 2,950	€ 3,401	-€ 451
	Follow-up costs	€ 55	€ 111	-€ 56
	Transport costs	€ 40	€ 48	-€ 8
	Costs due to productivity loss	€ 581	€ 713	-€ 132
Recurrent disease – distant metastases	Diagnostic costs	€ 622	€ 828	-€ 206
	Treatment costs	€ 12,890	€ 17,146	-€ 4,256
	Follow-up costs	€ 221	€ 450	-€ 229
	Transport costs	€ 193	€ 263	-€ 70
	Costs due to productivity loss	€ 2,490	€ 3,351	-€ 861
Breast cancer death	End of life costs	€ 3,986	€ 3,986	€ 0
	Costs due to productivity loss	€ 4,081	€ 4,081	€ 0
	Total costs	**€ 34,296**	**€ 39,997**	**-€ 5,701**
Life-years (LYs)	LYs accrued in stable disease state	19.69	17.86	1.83
	LYs accrued in recurrent disease local state	0.35	0.71	-0.36
	LYs accrued in recurrent disease metastases state	1.42	2.88	-1.46
	Total LYs	**21.45**	**21.45**	**0.00**
Quality-adjusted life-years (QALYs)	QALYs accrued in stable disease state	15.81	14.34	1.47
	QALYs accrued in recurrent disease local state	0.25	0.51	-0.26
	QALYs accrued in recurrent disease metastases state	0.84	1.71	-0.87
	QALYs lost due to AE	-0.01	-0.01	0.00
	Total QALYs	**16.89**	**16.55**	**0.34**

Table 14 shows the average lifetime costs and effects per patient after starting tamoxifen treatment in the base case scenario for both strategies and their increments.

The base case incremental total cost of the PGx strategy compared to the SOC strategy is -€5,701 per patient. This means that costs are saved when using the PGx strategy. The treatment strategy based on genetic information entails additional costs both for genotyping the CYP2D6-enzyme and tamoxifen treatment due to the increase of the tamoxifen dose for the identified slow metabolizers. These additional costs, however, have a minor impact on the total incremental cost (€253 extra costs of the €5,701 total saved costs) . More importantly, the SOC strategy – standard tamoxifen dose for all patients - is less effective in a subset of patients, leading to more breast cancer recurrences. These additional recurrences are associated with considerable costs: high diagnostic and treatment costs, more visits to the GP/hospital and more hospital admissions, and a lot of lost time, causing productivity loss and transport costs. Especially the treatment of distant metastases is very expensive, which makes it the main component of the costs saved by the PGx strategy due to fewer recurrences (€4,256 of the €5,701 total saved costs). Other important contributors to the reduced costs are the treatment of local recurrences (€450) and the difference in costs due to productivity loss (€861) in the metastatic disease stage.

The base case incremental effects of PGx strategy compared to standard of care strategy, expressed in life-years (LYs) and quality-adjusted life-years (QALYs), are 0.00 and 0.34, respectively. No LYs are gained or lost as the overall survival is assumed to be the same in both strategies. More importantly, disease-free survival will increase by approximately one year and ten months (1.83 years) per patient when applying the PGx strategy. PGx strategy leads to better health outcomes in QALYs as patients remain disease-free for a more prolonged period. Thus, most of the QALYs gained are during stable disease (1.47) compensated by a loss of QALYs in recurrent disease (1.13), leading to an overall gain in QALYs of 0.34.

Incremental cost-effectiveness ratio (ICER)

Table 15: Incremental cost-effectiveness ratio (base case)

Treatment	Costs	QALY	LY
PGx strategy	€ 34,296	16.89	21.45
Standard of care strategy (SOC)	€ 39,997	16.55	21.45
Increment	-€ 5,701	0.34	0.00
ICER PGx vs SOC		-€16,719	

Tamoxifen treatment based on individuals' genetic information reduces costs and gains more QALYs compared to SOC. The incremental costs per QALY gained (ICER) is -€16,719. This means that applying the personalized strategy is cost-effective and dominates the standard of care strategy (cost-reducing and more effective) at a willingness to pay of €0.

4.2. Sensitivity analysis

Scenario analysis

Table 16: ICER for different distributions of the recurrence rate

	Incremental costs	Incremental QALYs	ICER QALY
Weibull	-€ 6,724	0.39	-€ 17,173
Lognormal	-€ 2,898	0.20	-€ 14,712
Loglogistic	-€ 3,419	0.23	-€ 15,149

Table 16 shows the ICERs for different distributions of the recurrence rate. Changing the distribution of the recurrence rate influences the ICER results. The PGx treatment strategy remains dominant over the standard of care strategy (cost-reducing and better health outcomes) for the various distributions. When changing to a Weibull distribution, the PGx strategy saves slightly more costs and gains slightly more QALYS, resulting in a somewhat better, thus more negative ICER, than the ICER of the base case. A lognormal and loglogistic distribution for the recurrence probabilities leads to moderately lower incremental costs (fewer costs reduced) and lower QALYs gained, resulting in a worse, thus less negative ICER compared to the base case scenario.

Deterministic sensitivity analysis

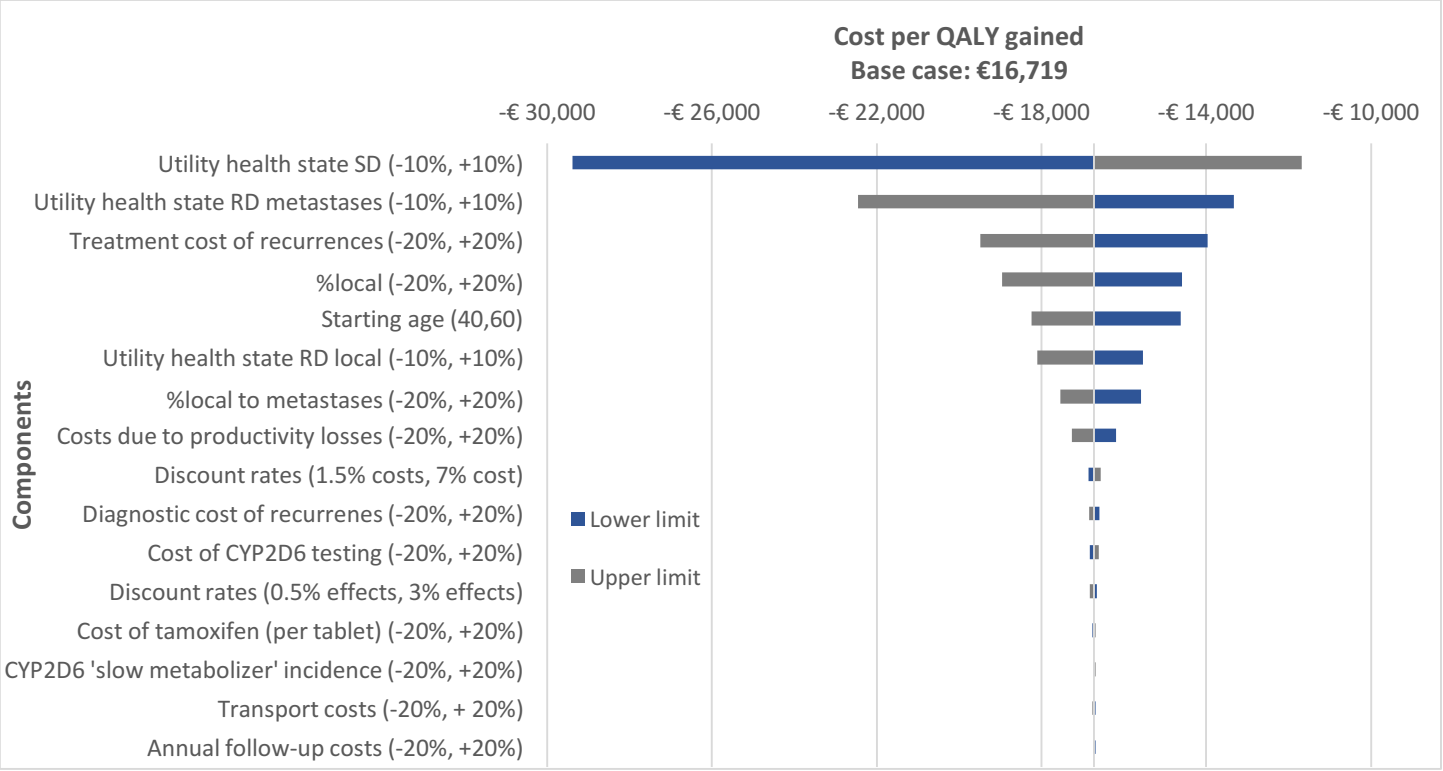


Figure 5: Tornado diagram

SD, stable disease ; RD, recurrent disease

Fig.5 shows the results from the one-way sensitivity analysis (tornado diagram) (see also Appendix 11). Note that the ICER is negative due to the cost-reducing effect of the PGx strategy. No scenarios led to a positive ICER. The ICER is sensitive to the utility values of the health states, especially to a lower utility value for stable disease leading to a more negative ICER. Changing the cost to treat recurrences by 20% had the second-largest impact, resulting in an ICER of over €2,000 lower or higher than in the base case scenario. A change of 20% in the percentages that recurrences are local recurrences or distant metastases affects the ICER moderately. If the percentage of recurrences with metastases would be 20% higher than in the base case, the ICER will be about €2,000 lower (more negative i.e. favorable) because more metastases - which entail high costs and a lower quality of life - are avoided. Cost-effectiveness is also slightly sensitive to the starting age of tamoxifen treatment (entry age in the model), with a more negative (i.e. favorable) ICER for women aged 60 compared to the base case (50 years).

Probabilistic sensitivity analysis (PSA)

The results of the PSA are displayed in Table 17 and visualized in a cost-effectiveness plane (CE-plane, Fig.6) and a cost-effectiveness acceptability curve (CEAC, Fig.7).

Table 17: Mean results PSA

	Mean Costs (SE)	Incremental Costs (95% CI)	Mean Effectiveness (LY)	Incremental LY (95% CI)	Mean effectiveness (QALY)	Incremental QALY (95% CI)
PGx	€34,538.49 (€4,092.14)	- €5,402.69 (-€12,685.13 – €989.07	21.46 (0.33)	0	16.87 (0.51)	0.32 (-0.04 – 0.78)
SOC	€39,941.19 (€3,841.03)		21.46 (0.33)		16.55 (0.51)	

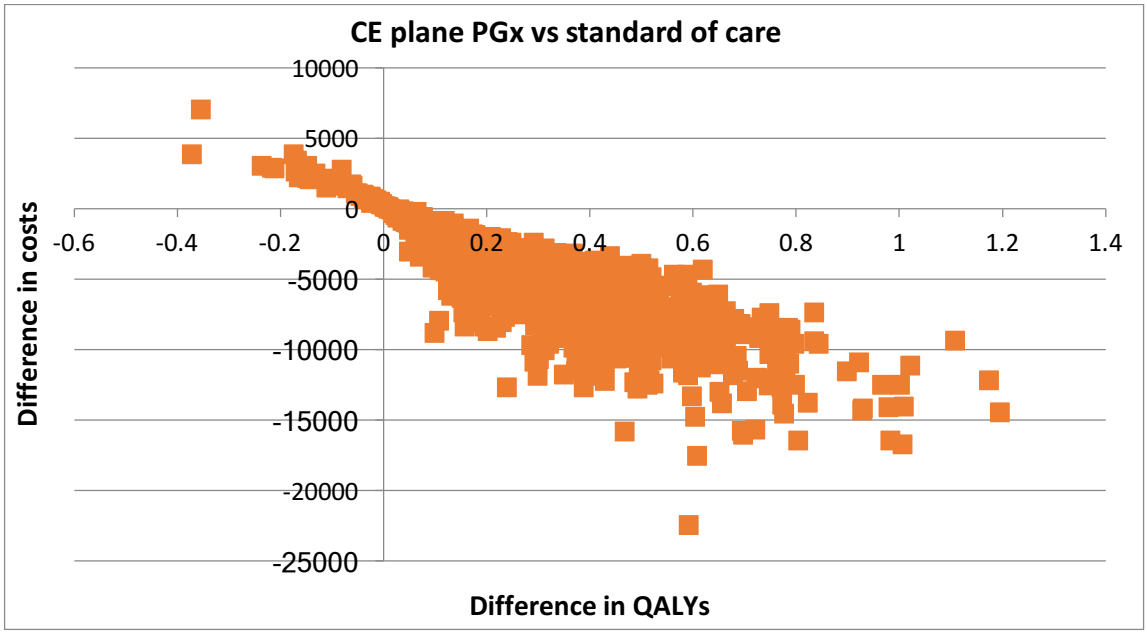


Figure 6: Cost-effectiveness plane PSA

Most ICERs (94%) are in the lower right quadrant of the CE-plane, which means that the PGx strategy is more effective and costs less than the standard of care strategy. Thus, the personalized strategy dominates the SOC strategy in most cases. Only some ICERs (5%) are located in the upper left quadrant of the CE-plane. The PGx strategy is dominated by the SOC strategy (more costs, less effective) for these cases. Also, a few ICERs (1%) are in the upper right quadrant. Whether these cases are cost-effective depends on the willingness to pay (WTP) for a QALY.

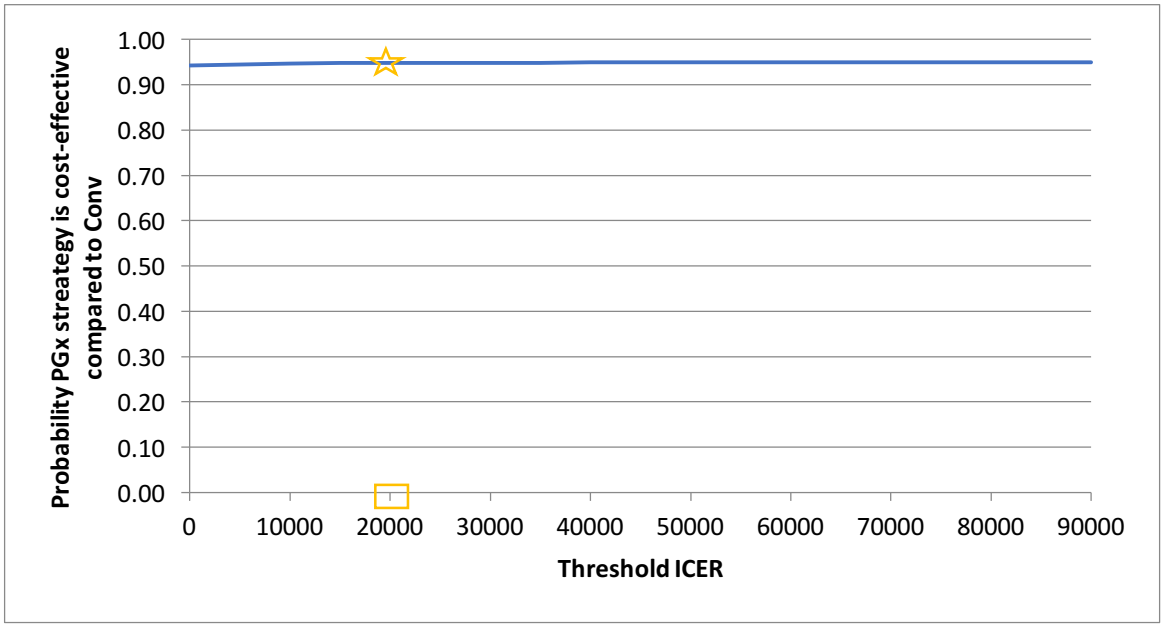


Figure 7: Cost-effectiveness acceptability curve PSA

Societal threshold

Probability at societal threshold

The cost-effectiveness acceptability curve (CEAC) indicates that at a WTP of € 0, the probability of tamoxifen treatment based on genotyping being cost-effective is 94%. This gradually increases to 95% at a WTP of €20,000 (provided WTP by ZIN). It does not converge to 100% because, in some cases, no benefits are achieved with the PGx strategy.

5. Discussion

Adjuvant tamoxifen treatment at the standard dose for women with early ER+ breast cancer has variable efficacy in patients (25,26). Germline genetic variations in the CYP2D6 liver enzyme may contribute to this response variability (25,26,35,36). Patients with a CYP2D6 'slow metabolizer' polymorphism - about 20% of the Dutch population (34) – have a higher risk of breast cancer recurrence at the standard dose of tamoxifen versus normal metabolizers, i.e. patients without the CYP2D6 'slow metabolizer' polymorphism (38). Increasing the tamoxifen dose (twofold) in these slow metabolizers would lead to similar plasma concentrations of the active metabolite of tamoxifen – endoxifen – and thus to the same therapeutic results as in normal metabolizers (45-48). Economic evaluations of tamoxifen treatment based on CYP2D6 genotyping are currently lacking, which in addition to clinical evidence is essential before it can be applied in practice (14,26). To fill this gap, a model-based cost-utility analysis was performed comparing the pharmacogenetic strategy versus the standard of care for women with an initial age of 50 years from a societal perspective with a lifetime horizon.

The current study results suggest that increasing the tamoxifen dose for women with ER+ breast cancer with a CYP2D6 'slow metabolizer' polymorphism is highly likely to be cost-effective compared to the current standard care (ICER: -€16,719/QALY gained). In most cases, this will be a cost-reducing intervention and dominant over the standard of care strategy, i.e. more effective (+0.34 QALYs gained) and less costly (-€5,701). Although the individual QALY gain is relatively small, the affected population is large, thus leading to a significant QALY gain at the macro level. The results are mainly due to the additional reduction in disease recurrences – which are expensive and reduce the quality of life – when using the personalized strategy. The deterministic sensitivity analysis shows that the ICER is most sensitive to the health state utilities and costs of treating recurrences. Probabilistic sensitivity analysis indicates that the cost-effectiveness's probability was 94% at a WTP of €0 per QALY and 95% at the societal WTP of €20,000 per QALY.

This evaluation is the first study to analyze the cost-effectiveness of tamoxifen treatment based on a patient's genetic background with a dose increase for women with a CYP2D6 'slow metabolizer' polymorphism. Two published studies (92,93) have comparable aims but result in significantly different ICERs. Methodological choices may differ between the studies, resulting in varying outcomes. The first one, Nuland et al. (92), investigated the cost-effectiveness of monitoring blood endoxifen (the active metabolite of tamoxifen) concentrations in Dutch ER+ breast cancer patients treated with tamoxifen. Patients with endoxifen concentrations - formed by conversion of tamoxifen by the CYP2D6-enzyme - below a certain threshold are eligible for a tamoxifen dose increase. In our study, endoxifen concentrations are guided based on the presence or absence of a CYP2D6 'slow metabolizer' polymorphism rather than measuring endoxifen levels directly, a technique called 'therapeutic drug monitoring' (annual drug monitoring costs in study by Nuland et al. (92): €113 and targeted CYP2D6 testing costs in our study: €184). Both studies reach the same conclusion: the personalized tamoxifen strategy (tamoxifen dose increase when needed) dominates (on average cost-reducing and more effective) the standard of care (20mg/day). The study by Nuland et al. was also conducted among the Dutch population with a lifetime horizon but from a healthcare payer perspective. They report an overall reduction of costs of €1,564 (lower than the saved costs of €5,701 in our study) and an increase in QALYs of 0.0115 per patient (lower than the gained QALYs in our study 0.34). This results in an ICER that is significantly lower (-€136,000/QALY gained) compared to our study (-€16,719/QALY gained) (probably due to utilities that are the main driver for the variation: tornado diagram). A similar Markov model is applied with three health states: disease-free survival, recurrent disease and death. The cycle length was set at 28 days. Patients enter the model at 53 years, similar as in our study (50yrs). In contrast to our model, Nuland et al. did not distinguish local from metastatic recurrence, which is somewhat surprising given the cost and utility difference between these stages. Overall survival was assumed to be similar for both strategies and was obtained in the same way as we did: adding the national background mortality (CBS) to the breast cancer-related mortality provided by the same EBCTCG meta-analysis (23). In contrast to our research, the breast cancer mortality curve was extrapolated using the method of Hoyle and Henley (66). Disease-free survival data was derived from the same EBCTCG trial (23) and adjusted for the hazard ratio for patients with low vs high concentrations of endoxifen (similar HR to the one used in our study between the genotypes). The utility values

for the health states were based on a sample of Swedish breast cancer patients but differed from our utility values, despite using the same type of measurement instrument (EQ-5D). Especially the utility value for recurrent disease was higher in the Swedish study (0.73 vs 0.71 for local recurrence and 0.59 for distant metastases in our study), probably because the disutility of distant metastases is not taken into account. Higher utility values of recurrent disease considerably affect the ICER, resulting in the more negative (i.e. favorable) ICER (univariate sensitivity analysis). It is unclear whether adverse events (AEs) are included in the study by Nuland et al.; they only state that the AEs are not dependent on the tamoxifen dose, which is a similar assumption as in our study. However, the AEs do not affect the ICER, so this does not explain their strongly negative ICER. The costs for the health states are based on a previous Dutch study. From the health care payer perspective, only medical costs should be included. The costs included in the study by Nuland et al (92) are the costs of the disease state (medical costs) and drug monitoring costs; thus, non-medical costs such as transportation costs and costs due to productivity loss, as we included for the societal perspective, are not considered. However, the ICER is not very sensitive to the non-medical cost categories.

Wei et al. (93) also performed a cost-effectiveness analysis to guide adjuvant hormone (tamoxifen or aromatase inhibitors) therapy based on genetic information but from the Chinese societal perspective. They conclude that the genotyping-based strategy is cost-effective in most cases. The reported ICER is substantially higher compared to our study (ICER $5,015/QALY gained vs ICER -€16,719/QALY gained), and the genotyping-based strategy is not cost-reducing, i.e. more effective (+3.582 QALYs gained) and more expensive ($17,966.65). This is probably due to the alternative treatment with aromatase inhibitors, which is more expensive compared to tamoxifen, that was used for patients with a CYP2D6 ‘slow metabolizer’ polymorphism. Design choices were partly different. Their Markov model consists of three health states (disease-free survival, recurrent disease and death), cycle length was one month and time horizon was set at 20 years. Disease-free and overall survival estimates were derived from a Chinese clinical trial with the same inclusion criteria as in our study, except that only postmenopausal women were included. The utility values for the health states are based on Swedish women with breast cancer (like Nuland et al. (92)), so higher utility values are used compared to our study, adding to a higher, more positive ICER. Adverse events were not included, although these differ for the treatment strategies since

aromatase inhibitors have different AEs than tamoxifen. The direct costs for stable disease and recurrent disease do not differ significantly (stable disease $4722 and recurrent disease $5402), which contrasts with our research. It is highly unlikely that the direct costs for the health states are so close. The treatment costs of recurrences, one of the main cost component in our study, is probably not included in their model, resulting in much lower costs related to recurrent disease. Consequently, the cost-benefit of avoiding recurrences with the personalized strategy is much lower, resulting in absence of a cost-reduction. Their study results are probably biased.

Strengths and limitations

One of the main strengths of our model is that it covers the societal perspective, i.e. including of transport costs and costs due to productivity loss, which is recommended by ZIN. In contrast to other studies (92,93), we distinguish between the types of recurrences (local and distant recurrences) because they involve different costs and quality of life. Moreover, Dutch-specific health state utilities are used instead of Nuland et al. (92) who used utilities from the Swedish population.

The cost-effectiveness study conducted in this thesis was based on several assumptions, and certain limitations must be recognized.

Firstly, the disease-free and overall survival estimates were based on two clinical studies (23,38). Despite the differences in mean age (pre- and postmenopausal), the recurrence rate curve is quite comparable. Both studies did not cover the entire lifetime (both follow-up of 15 years). In both strategies (PGx and standard of care), the extrapolated curves are below the observed curves (Appendix 1), resulting in an overestimation of the breast cancer recurrences. In reality, the recurrence rate will be lower resulting in more reduced costs and more QALYs gained leading to a more negative, i.e. favorable, ICER. However, the ICER is not sensitive to other distributions or small changes to the survival estimates and leads to the same conclusion of a cost-reducing strategy (scenario analysis). More recent and long-term follow-up data, preferably from a single Dutch clinical trial, could help to improve the accuracy of survival estimates. Secondly, our model – like the study by Nuland et al. (92) and Wei et al. (93) - did not consider the possibility of people relapsing a second time into the same local

recurrence state. Geurts et al (72) report that 6% of patients with a first local recurrence develop a second local recurrence and almost 55% of the patients with a previous second local recurrence develop a third recurrence. This could be included in the analysis.

Thirdly, utility values were extracted from Dutch studies (73). Disease-free patients have a lower utility value in the first year after surgery than in the years thereafter. The utility value for the recurrent disease was assumed to be constant over time. However, patients could also experience various utilities over the years in the recurrent state (e.g. higher utility score for the years following the entry of the local recurrent state i.e. after successful treatment) (73). The ICER proved very sensitive to changes in the health state utility values. Therefore, the validity of these parameters should be further investigated.

Fourth, assumptions are made about clinical practice, but reality may be different. We assumed that all patients receive the same follow-up care for the rest of their lives. In reality, the duration of the follow-up care is determined in consultation with the physician for each patient (21). A shorter follow-up period has a minimal effect on the ICER, as it affects the total costs of both strategies approximately the same. Moreover, patients with recurrences, especially those with metastases, will probably receive more extensive follow-up care (21). Higher follow-up costs for patients with recurrences result in a favorable, thus more negative ICER, as more costs are reduced with the PGx strategy. Moreover, some patients are diagnosed with fewer or more diagnostic tests (21), but no specific usage data of diagnostics have been found. A PET-CT scan could in the future replace all the diagnostic scans, but this is currently not the standard practice due to its high costs (94). The ICER however appears not very sensitive to changes in diagnostic costs (univariate sensitivity analysis).

Fifthly, almost all costs were taken from the study by Cocquyt et al. (86) except for hospital, day clinic and visit costs. These costs were obtained in our study by multiplying the frequencies used in the Belgian study with the Dutch unit costs (87). More accurate costs could be obtained if frequencies for the procedures for Dutch patients were found. Frederix et al. (95) suggest that the total cost of medical treatment and other resources per patient with metastatic breast cancer is slightly higher for Belgian patients than for Dutch patients. That means that the costs of treating recurrences are likely to be slightly higher than included

in the model, leading to a favorable, more negative ICER (more costs are saved with the PGx strategy).

Sixthly, the cost of genotyping CYP2D6 was based on targeted genetic testing for this specific enzyme (78). CYP2D6 however is only one of the components of the pharmacogenetic passport (PGx-passport). The cost for a PGx-passport (all 58 variants in 14 genes) is expected to be €1,378, this is an average of ErasmusMC and Gelre Ziekenhuis Apeldoorn (78). Using this cost for a PGx-Passport instead of the cost for targeted CYP2D6 testing (€184) in the cost-effectiveness analysis, results in a less negative (i.e. unfavorable) ICER (-€13,219/QALY gained vs -€16,719/QALY gained). However, the PGx-strategy remains a cost-reducing intervention and dominant over the standard of care strategy. On the other hand, the PGx-Passport in the future can be used for all drugs with a recognized drug-gene interaction, making the cost of genotyping CYP2D6 almost negligible with subsequently a slightly improved ICER.

It should also be noted that only the two most severe AEs were included in the model: thromboembolic events and endometrial cancer. If all tamoxifen-related AEs are included, a complete overview is obtained for the disutilities and costs related to AEs. It is unlikely that this limitation has biased the estimated ICER, as AEs, and the associated costs and utilities, are identical for both treatment strategies.

Validity and reliability

Internal validity of the input data is addressed above. Moreover, we assumed a fixed cohort of women with an initial age of 50 years, but entry into the cohort will be somewhat earlier, possible somewhat later (national breast cancer screening in the Netherlands starts at age 50). This means that in reality the onset is variable

The results must be interpreted carefully to generalize to other countries, as many of the parameters are country- and health-system -specific, and other countries use (sometimes or partly) different protocols than the Netherlands, resulting in different use of care. In addition, even with the same age and stage of illness, the valuation of health status can differ between countries. Furthermore, an interesting future field of research is the analysis of the cost-effectiveness of genotyping-based hormone treatment for postmenopausal women as

opposed to premenopausal women in the current study. For postmenopausal women with CYP2D6 'slow metabolizer' enzyme, an alternative treatment with aromatase inhibitors is a possible alternative.

Any issues with validity and reliability were addressed with the PSA, so the results can still be considered robust.

Further research and recommendations

Further clinical research is also recommended to expand the knowledge and relevance of CYP2D6 variants in the field of pharmacogenetics. It is important to note that the CYP2D6-enzyme is highly polymorphic (more than 80 variants, (34)). However, the effect of many of these variants on enzyme activity is not yet known and therefore, they are often not genotyped in trials. As a result, the control group (normal metabolizers) still contains many variations in enzyme activity. The benefit of a genotyping-based strategy may increase as the knowledge of CYP2D6 variants on enzyme activity deepens.

Based on the results, we advise healthcare professionals and healthcare policymakers to implement pharmacogenetic information (PGx-Passport) in daily routine care. It should be noted that cost-effectiveness is not the only outcome that will be considered in the decision whether or not to implement PGx testing or the PGx-Passport information in routine care. However, introducing PGx testing and personalized treatment based on genetic information (PGx-Passport) into routine care poses – next to the analysis of cost-effectiveness – several other challenges. The most important one will be the proper and ethical use (various aspects on data privacy) of an individual's genetic information. This is expected to be the subject of a broad social debate.

-

6. References

1. Strachan T, Goodship J, Chinnery P. Genetics and Genomics in Medicine. Boca Raton, FL: CRC Press; 2014.
2. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352(21):2211–21.
3. Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, et al. Pharmacogenomics. Lancet. 2019;394(10197):521–32.
4. Plöthner M, Ribbentrop D, Hartman J-P, Frank M. Cost-effectiveness of pharmacogenomic and pharmacogenetic test-guided personalized therapies: A systematic review of the approved active substances for personalized medicine in Germany. Adv Ther. 2016;33(9):1461–80.
5. Ahmed S, Zhou Z, Zhou J, Chen S-Q. Pharmacogenomics of drug metabolizing enzymes and transporters: Relevance to precision medicine. Genomics Proteomics Bioinformatics. 2016;14(5):298–313.
6. Westbrook K, Stearns V. Pharmacogenomics of breast cancer therapy: an update. Pharmacol Ther. 2013;139(1):1–11.
7. Chandra R. The role of pharmacogenomics in precision medicine [Internet]. Mlo-online.com. 2017 [cited 2021 Feb 21]. Available from: https://www.mlo-online.com/continuing-education/article/13009247/the-role-of-pharmacogenomics-in-precision-medicine
8. Ensom MH, Chang TK, Patel P. Pharmacogenetics: the therapeutic drug monitoring of the future?: The therapeutic drug monitoring of the future? Clin Pharmacokinet. 2001;40(11):783–802.
9. Haycox A, Pirmohamed M, McLeod C, Houten R, Richards S. Through a glass darkly: economics and personalised medicine. Pharmacoeconomics. 2014;32(11):1055–61.
10. KNMP. Pharmacogenetics [Internet]. Knmp.nl. 2020 [cited 2021 Feb 21]. Available from: https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1
11. Weitzel KW, Cavallari LH, Lesko LJ. Preemptive panel-based pharmacogenetic testing: The time is now. Pharm Res. 2017;34(8):1551–5.
12. Samwald M, Xu H, Blagec K, Empey PE, Malone DC, Ahmed SM, et al. Incidence of exposure of patients in the United States to multiple drugs for which pharmacogenomic guidelines are available. PLoS One. 2016;11(10):e0164972.
13. van der Wouden CH, van Rhenen MH, Jama WOM, Ingelman-Sundberg M, Lauschke VM, Konta L, et al. Development of the PGx-Passport: A panel of actionable germline genetic variants for pre-emptive pharmacogenetic testing. Clin Pharmacol Ther. 2019;106(4):866–73.
14. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? Pharmacogenomics J. 2017;17(5):395–402.

15. Kasztura M, Richard A, Bempong N-E, Loncar D, Flahault A. Cost-effectiveness of precision medicine: a scoping review. Int J Public Health. 2019;64(9):1261–71.
16. Kanker [Internet]. Volksgezondheidenzorg.info. [cited 2021 Jun 6]. Available from: https://www.volksgezondheidenzorg.info/onderwerp/kanker/cijfers-context/sterfte-en-overleving
17. Apotheek.nl [Internet]. Apotheek.nl. [cited 2021 May 5]. Available from: https://www.apotheek.nl/klachten-ziektes/kanker
18. Yu B, O'Toole SA, Trent RJ. Somatic DNA mutation analysis in targeted therapy of solid tumours. Transl Pediatr. 2015;4(2):125–38
19. IKNL. Kerncijfers over borstkanker uit de Nederlandse Kankerregistratie [Internet]. Iknl.nl. [cited 2021 Feb 21]. Available from: https://iknl.nl/nieuws/2020/kerncijfers-over-borstkanker-uit-de-nederlandse
20. Borstkanker [Internet]. Volksgezondheidenzorg.info. [cited 2021 May 5]. Available from: https://www.volksgezondheidenzorg.info/onderwerp/borstkanker/cijfers-context/huidige-situatie
21. Guideline D, 2. V. Breast cancer [Internet]. Oncoline.nl. [cited 2021 May 5]. Available from: https://www.oncoline.nl/uploaded/docs/mammacarcinoom/Dutch%20Breast%20Cancer%20Guideline%202012.pdf
22. Federatie medisch specialisten. Borstkanker - Tamoxifen - Richtlijn - Richtlijnendatabase [Internet]. Richtlijnendatabase.nl. [cited 2021 Jun 6]. Available from: https://richtlijnendatabase.nl/richtlijn/borstkanker/adjuvante_systemische_therapie/endocriene_therapie/tamoxifen.html
23. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378(9793):771–84.
24. Lumachi F, Santeufemia DA, Basso SM. Current medical treatment of estrogen receptor-positive breast cancer. World J Biol Chem. 2015;6(3):231–9.
25. Drögemöller BI, Wright GEB, Shih J, Monzon JG, Gelmon KA, Ross CJD, et al. CYP2D6 as a treatment decision aid for ER-positive non-metastatic breast cancer patients: a systematic review with accompanying clinical practice guidelines. Breast Cancer Res Treat. 2019;173(3):521–32.
26. Fleeman N, Martin Saborido C, Payne K, Boland A, Dickson R, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review. Health Technol Assess. 2011;15(33):1–102.
27. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353(26):2747–57.
28. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717

29. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JGM, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002;359(9324):2131–9.

30. van de Velde CJH, Rea D, Seynaeve C, Putter H, Hasenburg A, Vannetzel J-M, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet. 2011;377(9762):321–31.

31. Rioux PP. Clinical trials in pharmacogenetics and pharmacogenomics: methods and applications. Am J Health Syst Pharm. 2000;57(9):887–98; quiz 899–901.

32. Mancinelli L, Cronin M, Sadée W. Pharmacogenomics: the promise of personalized medicine. AAPS PharmSci. 2000;2(1):E4.

33. Hess P, Cooper D. Impact of pharmacogenomics on the clinical laboratory. Mol Diagn. 1999;4(4):289–98.

34. Algemene achtergrondtekst Farmacogenetica - CYP2D6 [Internet]. Knmp.nl. [cited 2021 May 31]. Available from: https://www.knmp.nl/downloads/g-standaard/farmacogenetica/achtergrondtekst-Farmacogenetica-CYP2D6-feb2020.pdf

35. Hertz DL, Rae JM. One step at a time: CYP2D6 guided tamoxifen treatment awaits convincing evidence of clinical validity. Pharmacogenomics. 2016;17(8):823–6.

36. Mulder TAM, de With M, Del Re M, Danesi R, Mathijssen RHJ, van Schaik RHN. Clinical CYP2D6 genotyping to personalize adjuvant tamoxifen treatment in ER-positive breast cancer patients: Current status of a controversy. Cancers (Basel). 2021;13(4):771.

37. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol. 2005;23(36):9312–8.

38. Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA. 2009;302(13):1429–36.

39. Bijl MJ, van Schaik RHN, Lammers LA, Hofman A, Vulto AG, van Gelder T, et al. The CYP2D6*4 polymorphism affects breast cancer survival in tamoxifen users. Breast Cancer Res Treat. 2009;118(1):125–30.

40. Nowell SA, Ahn J, Rae JM, Scheys JO, Trovato A, Sweeney C, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat. 2005;91(3):249–58.

41. Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, et al. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst. 2011;103(6):489–500.

42. Abraham JE, Maranian MJ, Driver KE, Platte R, Kalmyrzaev B, Baynes C, et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res. 2010;12(4):R64.

43. Center for Drug Evaluation, Research. Table of Pharmacogenomic Biomarkers [Internet]. Fda.gov. 2020 [cited 2021 Feb 21]. Available from: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
44. Knmp.nl. [cited 2021 May 5]. Available from: https://www.knmp.nl/downloads/pharmacogenetic-recommendations-3mei2021.pdf
45. Dezentjé VO, Opdam FL, Gelderblom H, Hartigh den J, Van der Straaten T, Vree R, et al. CYP2D6 genotype- and endoxifen-guided tamoxifen dose escalation increases endoxifen serum concentrations without increasing side effects. Breast Cancer Res Treat. 2015;153(3):583–90.
46. Welzen MEB, Dezentjé VO, van Schaik RHN, Colbers APH, Guchelaar H-J, van Erp NP, et al. The effect of tamoxifen dose increment in patients with impaired CYP2D6 activity. Ther Drug Monit. 2015;37(4):501–7.
47. Hertz DL, Deal A, Ibrahim JG, Walko CM, Weck KE, Anderson S, et al. Tamoxifen dose escalation in patients with diminished CYP2D6 activity normalizes endoxifen concentrations without increasing toxicity. Oncologist. 2016;21(7):795–803.
48. Kiyotani K, Mushiroda T, Imamura CK, Tanigawara Y, Hosono N, Kubo M, et al. Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients. Breast Cancer Res Treat. 2012;131(1):137–45.
49. Roberts RJ. Nucleic acid. In: Encyclopedia Britannica. 2020.
50. EMBL-EBI. What is genetic variation [Internet]. Ebi.ac.uk. [cited 2021 Jun 6]. Available from: https://www.ebi.ac.uk/training/online/courses/human-genetic-variation-introduction/what-is-genetic-variation/
51. Meyer UA, Zanger UM, Schwab M. Omics and drug response. Annu Rev Pharmacol Toxicol. 2013;53(1):475–502.
52. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics. 1998;8(4):283–9.
53. Wake DT, Ilbawi N, Dunnenberger HM, Hulick PJ. Pharmacogenomics. Med Clin North Am. 2019;103(6):977–90.
54. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. Annu Rev Genomics Hum Genet. 2014;15(1):349–70.
55. Vogel F. Moderne Probleme der Humangenetik. In: Ergebnisse der Inneren Medizin und Kinderheilkunde. Berlin, Heidelberg: Springer Berlin Heidelberg; 1959. p. 52–125.
56. Evans GA. The human genome project: Applications in the diagnosis and treatment of neurologic disease. Arch Neurol. 1998;55(10):1287.
57. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011;89(5):662–73.
58. Schwarz UI, Gulilat M, Kim RB. The role of next-generation sequencing in pharmacogenetics and pharmacogenomics. Cold Spring Harb Perspect Med. 2019;9(2):a033027.

59. Instituut Verantwoord Medicijngebruik [Internet]. Medicijngebruik.nl. [cited 2021 Jun 6]. Available from: https://www.medicijngebruik.nl/nieuwe-geneesmiddelen/column/2655/farmacogenetica--het-dna-paspoort-voor-medicatie-op-maat

60. Sitsen JMA, Abdullah-Koolmees H. Farmacogenetica. In: Geneeskundig Jaarboek 2021. Houten: Bohn Stafleu van Loghum; 2021. p. 802–5.

61. Erasmus MC. Farmacogenetica [Internet]. Erasmusmc.nl. [cited 2021 May 31]. Available from: https://www.erasmusmc.nl/nl-nl/patientenzorg/laboratoriumspecialismen/farmacogenetica

62. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. London, England: Oxford University Press; 2015.

63. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. London, England: Oxford University Press; 2006.

64. Guide to the methods of technology appraisal 2013 | Guidance | NICE. [cited 2021 May 8]; Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword

65. Ministerie van Volksgezondheid W en S. Richtlijnen voor economische evaluatie [Internet]. Zorginstituutnederland.nl. 2016 [cited 2021 Jun 6]. Available from: https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie

66. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011;11(1):139.

67. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. Health Policy. 2018;122(6):621–9.

68. Centraal Bureau voor de Statistiek. Consumer prices; price index 2015=100.

69. Overlevingscijfers van borstkanker [Internet]. Kanker.nl. [cited 2021 Jun 7]. Available from: https://www.kanker.nl/kankersoorten/borstkanker/algemeen/overlevingscijfers-borstkanker

70. Hakkaart-van Roijen, L., Van der Linden, N., Bouwmans, C., Kanters, T., & Tan, S. S. Handleiding voor kostenonderzoek: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015

71. Sterftekans – Kansberekeningen [Internet]. Kansberekeningen.nl. [cited 2021 May 31]. Available from: https://www.kansberekeningen.nl/sterftekans/

72. Geurts YM, Witteveen A, Bretveld R, Poortmans PM, Sonke GS, Strobbe LJA, et al. Patterns and predictors of first and subsequent recurrence in women with early breast cancer. Breast Cancer Res Treat. 2017;165(3):709–20.

73. Seferina SC, Ramaekers BLT, de Boer M, Dercksen MW, van den Berkmortel F, van Kampen RJW, et al. Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: A study of the Southeast Netherlands Breast Cancer Consortium. Oncotarget. 2017;8(45):79223–33.

74. Revisie richtlijn borstkanker [Internet]. Oncoline.nl. [cited 2021 May 31]. Available from: https://www.oncoline.nl/uploaded/docs/mammacarcinoom/Conceptstukken_RL_borstkanker_commentaarronde_mei_2017.pdf?u=1PFhSn
75. Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies for breast cancer in post-menopausal women: sequential tamoxifen-exemestane and upfront anastrozole. Breast Cancer Res Treat. 2007;101(3):325–33.
76. Locadia M, Bossuyt PMM, Stalmeier PFM, Sprangers MAG, van Dongen CJJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost. 2004;92(6):1336–41.
77. Korfage IJ, Essink-Bot M-L, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radiat Oncol Biol Phys. 2009;73(5):1501–9.
78. Erasmus MC. Farmacogenetica [Internet]. Erasmusmc.nl. [cited 2021 May 31]. Available from: https://www.erasmusmc.nl/nl-nl/patientenzorg/laboratoriumspecialismen/farmacogenetica
79. Medicijnkosten.nl [Internet]. Medicijnkosten.nl. [cited 2021 May 31]. Available from: https://www.medicijnkosten.nl/
80. Bijlage 1 bij TB/CU-7041-04 Tarievenlijst Eerstelijnsdiagnostiek - Nederlandse Zorgautoriteit [Internet]. Overheid.nl. [cited 2021 Jun 7]. Available from: https://puc.overheid.nl/nza/doc/PUC_11745_22/
81. Stevanovic J. Pharmacoeconomics of cardiovascular disease prevention. University of Groningen; 2015.
82. Ten Cate-Hoek AJ, Toll DB, Büller HR, Hoes AW, Moons KGM, Oudega R, et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. J Thromb Haemost. 2009;7(12):2042–9.
83. Ballegooijen M. Effects and costs of cervical cancer screening. Erasmus University Rotterdam; 1998.
84. Laarakker C, Nak W. Kanker.nl. [cited 2021 May 31]. Available from: https://www.kanker.nl/sites/default/files/library_files/14107/Nieuw....de_PSMA_PET_scan.pdf
85. Timmers JM, den Heeten GJ, Adang EM, Otten JD, Verbeek AL, Broeders MJ. Dutch digital breast cancer screening: implications for breast cancer care. Eur J Public Health. 2012;22(6):925–9.
86. Cocquyt V, Moeremans K, Annemans L, Clarys P, Van Belle S. Long-term medical costs of postmenopausal breast cancer therapy. Ann Oncol. 2003;14(7):1057–63.
87. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PLoS One. 2017;12(11):e0187477.
88. Schneider PP, Pouwels XGLV, Passos VL, Ramaekers BLT, Geurts SME, Ibragimova KIE, et al. Variability of cost trajectories over the last year of life in patients with advanced breast cancer in the Netherlands. PLoS One. 2020;15(4):e0230909.

89. redactie. Dit ben jij kwijt aan parkeren bij jouw ziekenhuis, bezoekers en patiënten betalen zich soms blauw [Internet]. De Stentor. 2019 [cited 2021 Jun 7]. Available from: https://www.destentor.nl/zwolle/dit-ben-jij-kwijt-aan-parkeren-bij-jouw-ziekenhuis-bezoekers-en-patienten-betalen-zich-soms-blauw~aee3b3d9/

90. Vemer P, Corro Ramos I, van Voorn GAK, Al MJ, Feenstra TL. AdViSHE: A validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics. 2016;34(4):349–61.

91. Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, Al M. TECH-VER: A verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics. 2019;37(11):1391–408.

92. van Nuland M, Vreman RA, Ten Ham RMT, de Vries Schultink AHM, Rosing H, Schellens JHM, et al. Cost-effectiveness of monitoring endoxifen levels in breast cancer patients adjuvantly treated with tamoxifen. Breast Cancer Res Treat. 2018;172(1):143–50.

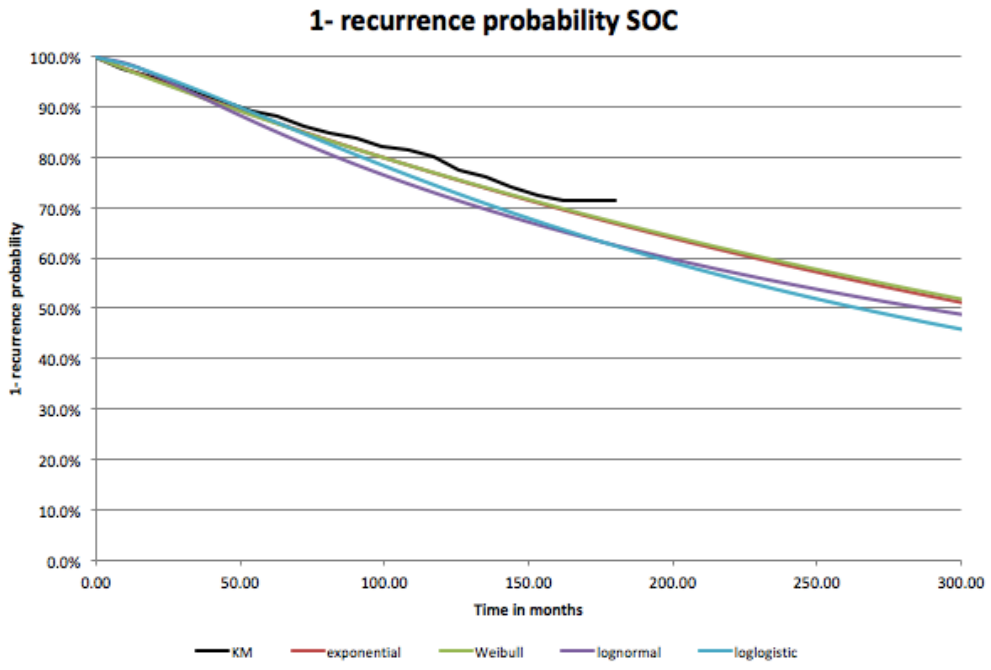
93. Wei X, Sun H, Zhuang J, Weng X, Zheng B, Lin Q, et al. Cost-effectiveness analysis of CYP2D6*10 pharmacogenetic testing to guide the adjuvant endocrine therapy for postmenopausal women with estrogen receptor positive early breast cancer in China. Clin Drug Investig. 2020;40(1):25–32.

94. Zuyderland.nl. [cited 2021 May 31]. Available from: https://www.zuyderland.nl/wp-content/uploads/2016/10/535-A4-Internet-folder-zuyderland-PETCT-scan-Nucleaire-geneeskunde.pdf

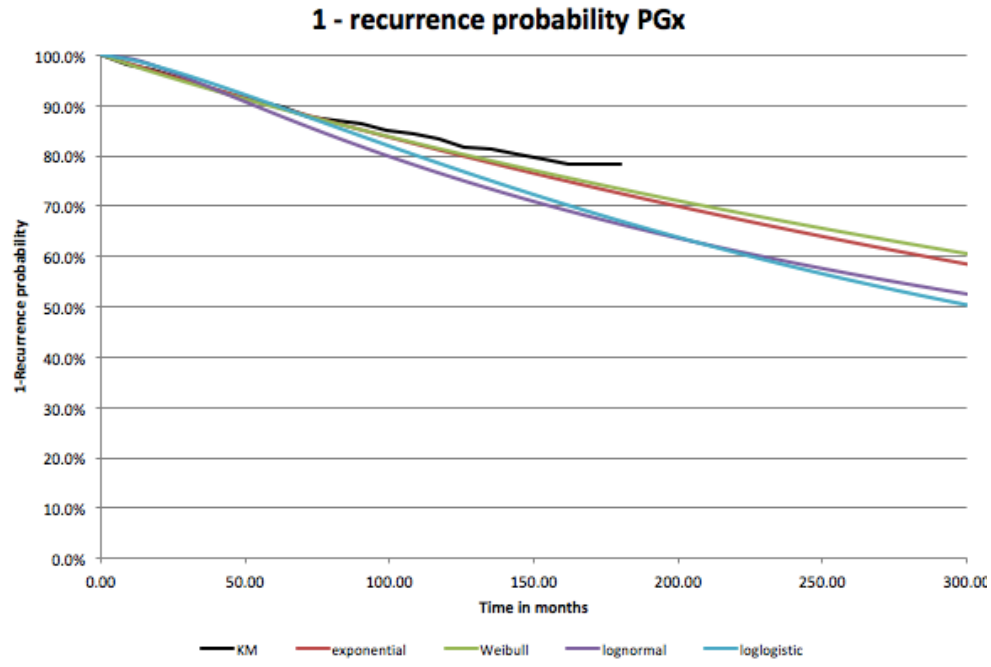
95. Frederix GWJ, Severens JL, Hövels AM, van Hasselt JGC, Hooiveld MJJ, Neven P, et al. Real world cost of human epidermal receptor 2-positive metastatic breast cancer patients: a longitudinal incidence-based observational costing study in the Netherlands and Belgium: HER-2-positive metastatic breast cancer cost. Eur J Cancer Care (Engl). 2015;24(3):340–54.

7. Appendix

Appendix 1: KM curves and parametric distributions for recurrence probabilities

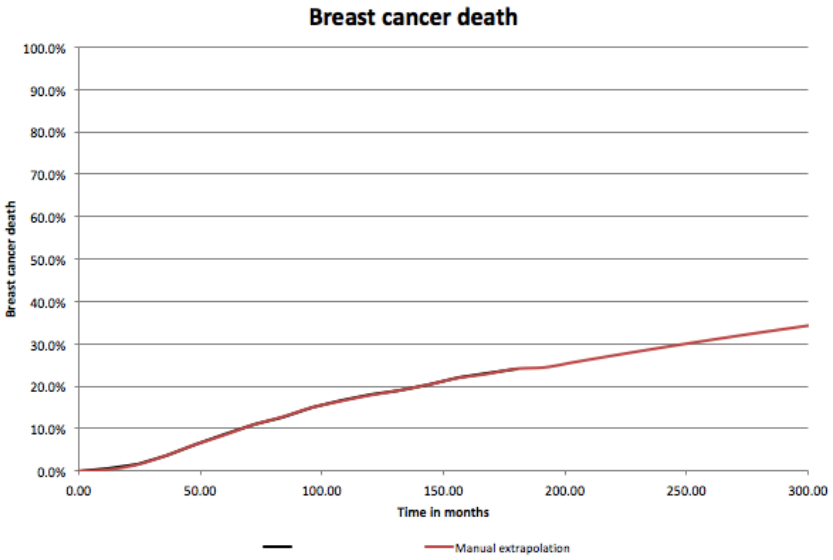


Source observed data: Schroth et al. (38)



Source observed data: Schroth et al. (38)

Appendix 2: Kaplan Meier curve and manual extrapolation breast cancer mortality



Source observed data: EBCTCG trial (23)

Appendix 3: Average costs per cycle per patient for the different cost categories

	Cost category		
	Parameter	**Average cost per cycle per patient**	**Cycle**
Stable disease	CYP2D6 testing[a]	€184.50	Cycle 1
	Drug acquisition costs[b]	€91.25 (SOC) ; €102.20 (PGx)	Cycle 1-5
	AE costs[c]	€539.05	Cycle 1
	Follow-up costs[d]	€189.29 (cycle1-5); €126.57 (cycle>5)	All cycles
	Transport costs	€6.00	All cycles
	Costs due to productivity loss[e]	€136.70	All cycles
Recurrent disease – local recurrence	Diagnostic costs	€505.46	Cycle 1
	Treatment costs	€20,227.94	Cycle 1
	Follow-up costs	€157.93	All cycles
	Transport costs	€261.03 (cycle 1); €6.00 (all cycles)	All cycles
	Costs due to productivity loss[e]	€7,044.04(cycle1);€136.70(all cycles)	All cycles
Recurrent disease – distant metastases	Diagnostic costs	€1,293.19	Cycle 1
	Treatment costs	€26,783.37	Cycle 1
	Follow-up costs	€157.93	All cycles
	Transport costs	€383.71 (cycle 1); €6.00 (all cycles)	All cycles
	Costs due to productivity loss[e]	€10,479.26 (cycle 1); €136.70	All cycles
Breast cancer death	End of life costs	€9,301.66	Cycle 1
	Costs due to productivity loss[e]	€16,303.74	All cycles

[a] only for PGx strategy
[b] Different for PGx and SOC strategy
[c] AEs related to tamoxifen treatment
[d] cycle 1-5 clinical examination by oncologist, cycle >5 clinical examination by GP
[e] until retirement age (67)

Appendix 4: Treatment costs for thromboembolic events (Ten Cate-Hoek et al., 2009 (82))

Parameter	Unit costs	Resource use	se	Distribution	Source
Event DVT					
GP consultation	€29.60				Dutch Cost Manual
# of GP consultations		0.83	0.30	gamma	AMUSE
Home care compression therapy	€480.62				AMUSE. Dutch Cost Manual
LMWH 7 days	€66.68				Pharmacotherapeutic Compass
Coumarins 6 months	€85.61				Pharmacotherapeutic Compass
specialist visit	€57.12				Dutch Cost Manual
# control visits specialist		2.79	0.84	gamma	AMUSE
INR control visit	€8.46				Thrombosis Service
# INR control visits		16.38	1.28	gamma	AMUSE
compression stockings	€60.38				Health care insurance company
Hospital day	€485.52				Dutch cost manual
# hospital days		0.63	0.11	gamma	AMUSE
Total costs	**€1322.45**				
Event PE					
GP consultation	€29.60				Dutch Cost Manual
# of GP consultations		1.42	1.07	gamma	AMUSE
ER visit	€141.78				Dutch Cost Manual
CT thorax	€132.35				Dutch Cost Manual
ECG	€25.41				Dutch Cost Manual
Blood draw	€10.64				Dutch Cost Manual
Lab procedures	€1.78				Dutch Cost Manual
# lab procedures		5.00			Haematology (3), clinical chemistry (2); expert opinion
Hospital day	€485.52				Dutch Cost Manual
# hospital days		7.00			Expert opinion
LMWH 7 days	€66.68				Pharmacotherapeutic Compass
Coumarins 6 months	€85.61				Pharmacotherapeutic Compass
# control visits specialist		2.79	0.84	gamma	AMUSE
# INR control visits		16.38	1.28	gamma	AMUSE
Total costs	**€4209.77**				

DVT: deep venous thrombosis; PE: Pulmonary emboli

Appendix 5: Treatment costs for endometrial cancer (Ballegooijen, 1998 (83))

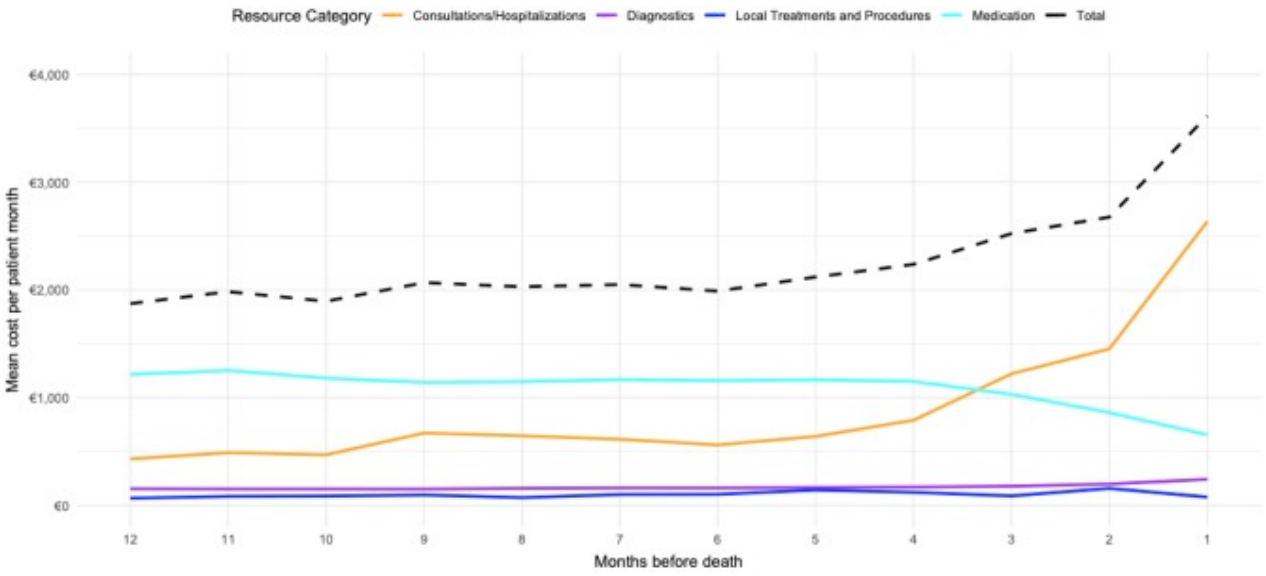
	Costs per patient (Dfl)		% Of total costs	
In-hospital care	20 350		70	
hospital days		12 690		43
intensive care		560		2
in-hospital procedures		7 100		24
Nursing home care	2 400		8	
Home care	6 440		22	
Total care	29 200		100	

Appendix 6: Hospital, day clinic and visit frequencies and costs for treatment of recurrences

	Breast cancer treatment costs (€)		
	Local recurrence Value (SE[a])	**Distant metastases Value (SE[a])**	**Source**
Hospital stay			
Unit cost/day	€514.78 (€102.96)	€514.78 (€102.96)	Kanters et al 2017
No. of days	10.02 (2.004)	16.45 (3.290)	Cocquyt 2003
Day clinic			
Unit cost/day	€298.49 (€59.70)	€298.49 (€59.70)	Kanters et al 2017, Hakkaart-van Roijen et al., 2016
No. of days	7.22 (1.444)	8.63 (1.726)	Cocquyt 2003
Visits			
Unit cost/day	€35.69 (€7.14)	€35.69 (€7.14)	Kanters et al 2017, Hakkaart-van Roijen et al., 2016
No. of visits	31.10 (6.220)	50.0 (10.0)	Cocquyt 2003

[a] SE based on 20% of the mean

Appendix 7: End of life costs per cost category (Schneider et al. 2017 (88))



Appendix 8: Hospital, day clinic and visit frequencies per health state

Frequencies hospital stay, day clinic, visits	Value (SE[a])	Source
SD – visits		
Annual follow-up	2 (0.40)	Assumption
RD local recurrence – hospital stay		
Treatment	10.02 (2.004)	Cocquyt 2003
RD local recurrence – day clinic		
Treatment	7.22 (1.444)	Cocquyt 2003
RD local recurrence - visit		
Diagnostics	3 (0.60)	Assumption
Treatment	31.10 (6.222)	Cocquyt 2003
Annual follow-up	2 (0.40)	Assumption
RD distant metastases – hospital stay		
Treatment	16.45 (3.29)	Cocquyt 2003
RD distant metastases – day clinic		
Treatment	8.63 (1.726)	Cocquyt 2003
RD distant metastases visits		
Diagnostics	3 (0.60)	Assumption
Treatment	50.00 (10.00)	Cocquyt 2003
Annual follow-up (year 5+)	2 (0.40)	Assumption
Breast cancer death day clinic/hospital stay	0	Assumption

[a] SE based on 20% of the mean

Appendix 9: Data for costs due to productivity losses

Productivity loss	Value (SE)	Source
Friction period in days	85 (8.5[b])	Hakkaart-van Roijen et al., 2016
Productivity costs per hour per women in paid employement	€31.60 (€6.83[a])	Hakkaart-van Roijen et al., 2016
Working hours per day	8	Hakkaart-van Roijen et al., 2016
Absence due to visit in hours	2	Assumption

[a] SE based on 20% of the mean
[b] SE based on 10% of the mean

Appendix 10: Data for transport costs

Transport costs	Value (SE)	Source
Average distance to hospital	7 (0.7[b])	Hakkaart-van Roijen et al., 2016
Average distance to GP	1.1 (0.11[b])	Hakkaart-van Roijen et al., 2016
Price car (per km)	€0.21 (€0.04[a])	Hakkaart-van Roijen et al., 2016
Parking costs car		
Hospital per day	€9.05 (€1.81[a])	Van Houwelingen & Hartmen 2019
Visit	€3.24 (€0.65[a])	Hakkaart-van Roijen et al., 2016
Price public transport	€0.21 (€0.04[a])	Hakkaart-van Roijen et al., 2016
No. travels per of trips	2	
Average length of hospital stay	3 (0.60[a])	
Proportion to care organization by car	80% (8%[b])	Assumption
Proportion to care organization by public transport	20% (2%[b])	Assumption

[a] SE based on 20% of the mean
[b] SE based on 10% of the mean

Appendix 11: Consumer price indexes

Consumer price index	Value (SE)	Source
2003-2004	1.30	CBS (2020) Consumer price indexes
2004-2005	1.70	CBS (2020) Consumer price indexes
2005-2006	1.10	CBS (2020) Consumer price indexes
2006-2007	1.60	CBS (2020) Consumer price indexes
2007-2008	2.50	CBS (2020) Consumer price indexes
2008-2009	1.20	CBS (2020) Consumer price indexes
2009-2010	1.30	CBS (2020) Consumer price indexes
2010-2011	2.30	CBS (2020) Consumer price indexes
2011-2012	2.50	CBS (2020) Consumer price indexes

2012-2013	2.50	CBS (2020) Consumer price indexes
2013-2014	1.00	CBS (2020) Consumer price indexes
2014-2015	0.60	CBS (2020) Consumer price indexes
2015-2016	0.30	CBS (2020) Consumer price indexes
2016-2017	1.40	CBS (2020) Consumer price indexes
2017-2018	1.70	CBS (2020) Consumer price indexes
2018-2019	2.60	CBS (2020) Consumer price indexes
2019-2020	1.30	CBS (2020) Consumer price indexes

Appendix 12: one-way sensitivity analysis

Component	Base input	Low input	High input	Base case ICER	Lower limit ICER	Upper limit ICER
Utility health state SD (-10%, +10%)	0.728 (SD cycle 1) 0.805 (SD cycle >1)	0.665 (SD cycle 1) 0.725 (SD cycle >1)	0.801 (SD cycle 1) 0.886 (SD cycle >1)	-€ 16,719	-€ 29,387	-€ 11,683
Utility health state RD metastases (-10%, +10%)	0.594	0.535	0.653	-€ 16,719	-€ 13,321	-€ 22,445
Treatment cost of recurrences (-20%, +20%)	€20,227.94 (local recurrence) €26,783.37 (metastases)	€16,182.35 (local recurrence) €21,426.70 (metastases)	€24,273.53 (local recurrence) €32,140.04 (distant metastases)	-€ 16,719	-€ 13,959	-€ 19,480
%local (-20%, +20%)	27.50%	22% local ; 78% metastases	33% local ; 67% metastases	-€ 16,719	-€ 14,595	-€ 18,956
Starting age (40,60)	50	40	60	-€ 16,719	-€ 14,619	-€ 18,246
Utility health state RD local (-10%, +10%)	0.717	0.645	0.788	-€ 16,719	-€ 15,539	-€ 18,094
%local to metastases (-20%, +20%)	28%	22%	34%	-€ 16,719	-€ 15,585	-€ 17,542
Costs due to productivity losses (-20%, +20%)	€136.70 (SD,RD all cycles) €7,044.04 (RD local cycle 1) €10,479.26 (RD metastases cycle 1) €16,403.74 (Breast cancer death)	€109.36 (SD,RD all cycles) €5,635.26 (RD local cycle 1) €8,383.41 (RD metastases cycle 1) €13,122.99 (Breast cancer death)	€164.04 (SD,RD all cycles) €8,452.85 (RD local cycle 1) €12,575.11 (RD metastases cycle 1) €19,684.49 (Breast cancer death)	-€ 16,719	-€ 16,185	-€ 17,254
Discount rates (1.5% costs, 7% cost)	4%	1.5% costs	7% costs	-€ 16,719	-€ 16,862	-€ 16,554
Diagnostic cost of recurrenes (-20%, +20%)	€505.46(local recurrence) €1,293.19 (distant metastases)	€404.37 (local recurrence) €1,034.55 (distant metastases)	€606.55 (local recurrence) €1,551.83 (distant metastases)	-€ 16,719	-€ 16,592	-€ 16,846
Cost of CYP2D6 testing (-20%, +20%)	€ 184.50	€ 147.60	€ 221.40	-€ 16,719	-€ 16,827	-€ 16,611
Discount rates (0.5% effects, 3% effects)	1.50%	0.5% effects	3% effects	-€ 16,719	-€ 16,652	-€ 16,819
Cost of tamoxifen (per tablet) (-20%, +20%)	€0.25 (tablet 20mg) €0.40 (tablet 40mg)	€0.2 (tablet 20mg) €0.32 (tablet 40mg)	€0.3 (tablet 20mg) €0.48 (tablet 40mg)	-€ 16,719	-€ 16,756	-€ 16,679
Transport costs (-20%, + 20%)	€6.00 (SD,RD all cycles) €261.03 (RD local cycle 1) €383.71 (RD metastases cycle 1)	€4.80 (SD,RD all cycles) €208.83 (RD local cycle 1) €306.97 (RD metastases cycle 1)	€7.21 (SD,RD all cycles) €313.24 (RD local cycle 1) €460.46 (RD metastases cycle 1)	-€ 16,719	-€ 16,680	-€ 16,758
Annual follow-up costs (-20%, +20%)	€189.29 (SD cycle 1-5) €126.57 (SD cycle >5) €157.93 (RD all cycles)	€151.43 (SD cycle 1-5) €101.25 (SD cycle >5) €126.34 (RD all cycles)	€227.15 (SD cycle 1-5) €151.88 (SD cycle >5) €189.52 (RD all cycles)	-€ 16,719	-€ 16,689	-€ 16,750