“EXPLORING MARKOV MODELING APPROACHES FOR THE HEALTH ECONOMIC ASSESSMENT OF CIRCULATING TUMOR CELLS IN THE MANAGEMENT OF METASTATIC PROSTATE CANCER PATIENTS”

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ABSTRACT

Objective: To investigate the applicability of methodological approaches in personalized (cancer) care, by using an early HTA case of the CTC trap medical device.

Methods: For this study, different Markov cohort models were developed for the purpose of early HTA of the CTC-trap as diagnostic and/or prognostic device in the diagnostic pathway of prostate cancer.

Results: The results demonstrate the difficulty of Markov modeling approaches in early HTA in personalized (cancer) care. Although, an indication that CTC-trap is a probable technology to use in the diagnostic pathway of prostate cancer, the evidence to substantiate this claim is difficult to obtain via Markov modeling. Due to multi-plural combination of treatments sequences, personalized medicine cannot apply the same simplifications and assumptions in straightforward intervention to golden standard comparisons.

Conclusion: Two main problems were identified when Markov modeling approaches for early modeling of CTC-trap in mCRPC were modeled: time-dependency in transition probabilities and the available patient level data to populate the models in early HTA. The simplifications applied in health economic assessments cause major uncertainty and, especially in personalized medicine, may lead to large variations in outcomes.

Keywords: Markov, Prostate Cancer, mCRPC, HTA, Decision modeling,

TABLE OF CONTENTS

1. INTRODUCTION

The impeding progress of finding "the cure" for cancer as medical-quest, goes hand in hand with rapidly changing healthcare around the world [2]. Under the influence of demographics, economic growth, improved access to health care and high turn-over of advanced medical technology, costs are rising in this evolving trend [3], [4]. For example, if the trend of increasing healthcare costs in the Netherlands continues, healthcare will consume 25% of the GDP in 2040 [5]. The health care system around the world is in need of innovation, and medical technology is one of the suggested solutions [6], [7]. Hence, the search for methods to treat and cure cancer uses the newest pharma- and medical technology knowledge.

1.1.Medical technology & HTA

The medical technology field is known as dynamic, capricious and equally as innovative as it is risky [8]. The enormous amount of investments in the product development creates an increased pressure to maximize profits [1]. To ensure the safety of products, minimize risk for patients and control market access, regulation of medical devices is required [9], [10]. It is of essential importance to the medtech stakeholders to make decisions at the appropriate stage, for which different methods of Health Technology Assessment (HTA) can be applied [1]. HTA is the evaluation of a new health technology and its effects and is aimed at informing decision making in health technologies [11]. "Early HTA" is defined by the International network of Agencies for Health Technology Assessment as an early study of the medical, economic, social, and ethical implications of the medical device to determine the potential for incremental value in healthcare [12]. Early-HTA takes place from the moment of idea generation for new innovations until clinical trials start, as shown in figure 1. Early-HTA provides early stage information to use in pre-market development stages of new innovations, aiming at optimal long-term results [13]. At the same time, HTA is used from the payers perspective to assess whether or not a new technology is cost-effective and does not incentivize cost increasing [7]. Economic evaluation, one of the most common form of HTA, is defined as two or more alternative interventions that are evaluated and compared on their costs and their (clinical) effects. As a result, the relative benefits and costs of each investigated alternative are compared [14] .

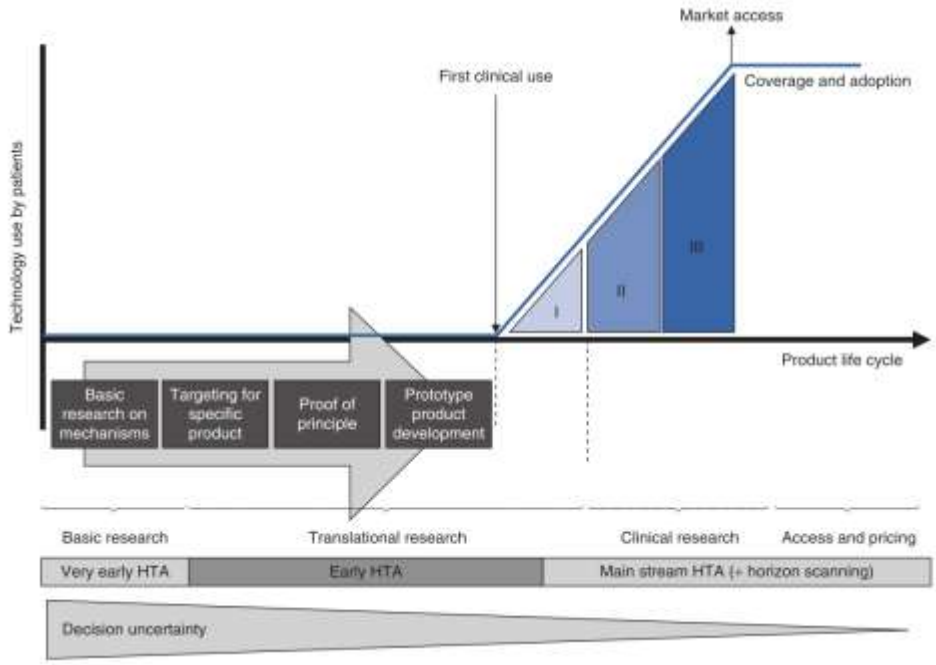

Figure 1. Flowchart of stages in medical devices development, where early-HTA is performed in the stages I. Basic Research and II. Translational Research. (Retrieved from IJzerman and Steuten, 2011 [1])

1.2.Prostate cancer

Malignant neoplasm, more commonly known as cancer, is a wide range of diseases with unregulated or uncontrollable growth of cells. Nowadays more than 200 different types of cancer are known that affects humans [15]. In 2012, 14.1 million new diagnoses and 8.2 million cancer deaths were estimated worldwide [16]. Malignancies that occur in the soft tissue of the prostate gland – located in the male reproductive system, surrounding the urethra just below the bladder - is known as prostate cancer (ICD-10 C61) [17]. Prostate cancer is one of the most occurring cancer in men in Europe [18], [19]. In the UK, prostate cancer is the most commonly diagnosed malignancy in men (25.0 % of cases), with an incidence of 41,736 in 2011 [20], [21]. Prostate cancer has a mortality of 10,793 in 2011, and counts for 13.0 % of all male deaths from malignancies [20], [22]. In the same year, 11,654 men in the Netherlands were diagnosed with prostate cancer and a corresponding 2,535 died [23].

Symptoms are often absent in the early stages of prostate cancer. If symptoms do occur, polyuria, pain during urination and the feeling of not being able to completely empty the bladder are most seen in clinic [17]. Treatment options for prostate cancer depend on several factors, including TNM staging and Gleason scoring, and range from surgery, radio therapy, hormone treatment to a combination of these treatments [17], [24]–[26]. Since the introduction of the prognostic biomarker Prostate-specific Antigen (PSA), the detection, and thus overall survival of prostate cancer, has increased rapidly [27]. The age standardized 5-year overall survival in the UK (measured 2007-2011) is 81.7 % [28]. Metastatic prostate cancer is characterized by the spread of malignancies outside the prostate gland, after initial treatment, and is most common in the lymph nodes. The malignancies are often found in bone-tissue and more rarely in soft tissue like lungs [17]. The age standardized 5-years survival of distant metastatic prostate cancer is less than 32.6 % [29].

Patients whose prostate cancer progresses into a metastatic stage, despite (hormonal) treatment, are known as metastatic Castration-resistant prostate cancer (mCRPC), previously known as ‘hormone refractory prostate cancer’ or ‘androgen independent prostate cancer’ [30]. CRPC is clinically presented by low testosterone level but with high levels of PSA and distant metastasis’, visible on CT-, MRI- or bone scans. Historically, the reported prognosis for mCRPC patients is 18-24 months of survival with deteriorating quality of life and the disease progressing firstly asymptomatic and secondly symptomatic [25], [26]. However, clinical experience indicates that new treatment options prolong the survival and improve the quality of life of patients by alleviating symptoms [31]–[35].

1.3.Circulating Tumor Cells

The main cause of mortality due to malignancies is (distant) tumor metastasis [36]. Metastases originate when tumor cells migrate from the initial tumor through the body via lymph or blood to proliferate at distant locations. The circulation through the bloodstream gives these cells the name Circulating Tumor Cells (CTC’s) [37], [38]. The ratio of CTC’s in the blood is very low, approximately 1 to 10 CTC’s per ML blood [39]. A portion of the CTC’s will develop into distant metastasis [40].

CTC’s can be isolated from the bloodstream and, due to their common origin, can provide essential information to be used for prognosis and diagnostic purposes [30], [37], [41]–[43]. By using CTC’s to track severity and test the efficacy of certain treatments, mCRPC patient could receive more targeted treatment aiming at improving survival and increasing their quality of life. And moreover, if biological properties of CTC’s can be analyzed in such a way that it serves as a

'liquid biopsy', CTC's could predict more precise the heterogeneous response to different drugs and treatments in different patients and, hence, can function as personalized medicine [44]–[46].

1.4. CTC-trap

Isolating CTC is extremely challenging and requires enrichment and separation from the surrounding cells [47]. CTC's identification is most common via molecular markers, in order to distinguish the CTC from other hematopoietic cells [48]. In recent years, several technologies became available for the detection of CTC's. The methods are merely based on filtration (size-based), density gradient and immune-magnetic properties [40], [47]–[49].

1) Filtration of CTC is possible in a simple step due to the small size of peripheral blood cells. After filtration the CTC can be stained with different markers to be identified. Despite the clinical studies, this method is not validated due to the catch of other large cells like leukocytes [50], [51].
2) Density gradient-based enrichment creates layers of cells in order of their density. By means of centrifugation, the layers can be identified where CTC will be, just as other mononuclear cells, just below the plasma layer [47], [52]. However, CTC can frequently be lost during the process as they migrate into the plasma [48], [51].
3) The last enrichment method, immonu-magnetic based is the most commonly used. However, the choice of specific markers is difficult due to the continuous change in antigens. Though CK, EpCAm, CD45 and BerEP4 are generally the most uses markers [47], [53]. In case of prostatic cancer, organ specific PSA staining can be used as well [51]. Currently, the only clinically validated, FDA approved, system is CellSearch™ system (Veridex) which works via EpCAM immunomagnetization [39], [40].

Despite the variety of CTC extraction technologies, hurdles exist in the current state of research and development. These hurdles include, definition of CTC's (i.e., each cancer has a specific CTC), automated identification, cellular viability and diagnostic performance characteristics as sensitivity and specificity [54].

CTC-trap, acronym for Circulating Tumor Cells TheRapeutic APheresis, is a new method to improve the use of CTC's in the clinical pathway. The CTC-trap uses both ummonucapture as size-based enumeration of CTC's from full blood, like plasma aphaeresis with returning of unused cells and fluids [40] (see figure 2). With this, the CTC-trap tries to improve the detection of CTC's compared to the current outcomes under the CellSearch method [55]. By increasing the volume of blood sample to 1 to 5 liters by aphaeresis instead of a static 7.5 ml as currently used at the CellSearch system, the CTC trap will provide a more effective and complete method to identify and extract CTC's in good quantities and viable for culturing [40]. Since the CellSearch detects CTC's in approximately (only) 50% of the patients with metastatic neoplasm's, the CTC-trap will allow the detection of (more) CTC's in more patients, ultimately leading to tailoring treatment [40], [49], [56].

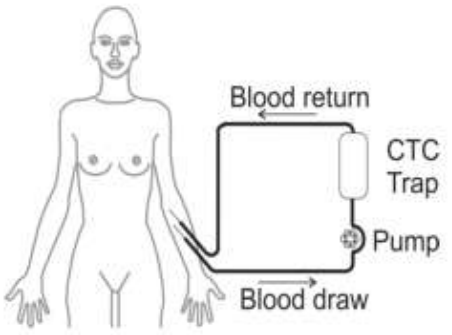

Figure 2. Schematic overview of CTC-trap (Retrieved from Barradas and Terstappen, 2013 [40])

1.5.New cancer therapies

Approximately 900 novel cancer drugs are currently under development by biopharmaceutical researchers [57]. These novel drug-based therapies are evolving fast. Also known as 'target drugs', these drugs target specific signaling pathways in oncogenic pathology [58]. In the last 5 years, Radium Ra-223 dichloride (Xofigo), Enzulatamide (Xtandi), Abiraterone acetate (Zytiga) and Cabazitaxel (Jevtana) received an FDA approval for the treatment of prostate cancer [59]. These drugs, however, are of significant costs. For example Enzalutamide - an oral androgen receptor signaling inhibitor that reduces de proliferation of PCa cells - costs EUR 3,432.07[1] for a 112 40mg capsules package [60]. Assuming a daily dose of 160 mg and an mean length of treatment of 8.5 months, this would be EUR 31,713[2] [61]. Due to the increased availability of drug therapies to choose from, and the cost of these drugs, it is of vital importance to be able to rapidly assess if the chosen therapy is effective [62].

1.6.Personalized Medicine

Personalized medicine seeks to stratify treatments as optimal as possible to ensure effective treatments and reduce unnecessary side effects and healthcare spending. Personalized medicine allows the increasing of the ability to choose an effective and timely treatment, while minimizing costs associated with ineffective treatments and avoidable adverse events [63]. The unique responsiveness to drugs is subject to our human genome. Genome sequencing and molecular diagnosing will enable tailoring of treatments. Personalized medicine is perceived by some as the potential solution for healthcare spending problems, amongst which the United States Food and Drug Administration [64]. On the other hand, skepticism exist on methodological issues in health economic outcomes research of personalized medicine [65]. Annemans, Redekop & Payne already identified 10 methodological challenges and possible solutions when it comes to health economic assessments of personalized medicine innovations [66].

1.7.Relevance

The treatment of, or in this case the (palliative) care and monotoring of mCRPC patients, is a case that fits the personalized medicine health economic assessment discussion. National authorities require solid evidence when it comes to market access, reimbursement and other regulatory purposes [64]. Though, it is a question whether the currently widely used HEA modeling approaches (e.g. Decision Tree and Markov Cohort Models) are still applicable in de complexity of personalized medicine.

Objective of this study is to investigate applicability of these methodological approaches by using an early HTA case of the CTC trap medical device. For this study, a Markov cohort model was developed for the purpose of early HTA of the CTC-trap as diagnostic and/or prognostic device in the diagnostic pathway of prostate cancer. As already shown in metastatic breast cancer, blood-based CTC's count can be a useful predictor of treatment efficacy [67]. If taken a parallel with metastatic breast cancer, and the knowledge that there is a clinically validated prognostic CTC assay for solid cancers like breast, colon and prostate cancer [54], CTC-trap could be used in the diagnostic pathway of prostate cancer and could contribute to a personalized medicine approach in prostate cancer care.

[1] £2,734.67 at exchange rate on 09/05/2014

[2] £25,269.00 at exchange rate on 09/05/2014

2. METHODS

This study is been carried out using a variety of methods. First, a literature study was performed to obtain solid background information on the latest scientific knowledge on the CTC trap, (metastatic) prostate cancer, and the Markov-model method in decision modeling in Health Economic Evaluation. Then, the clinical pathway was constructed to determine the possible points of improvement by implementing the CTC trap medical device. Thereafter, an analytical model for analyzing the health economic benefit and clinical usability was constructed.

2.1. Literature study

A literature study is performed to obtain the latest scientific knowledge on the background of the study. The literature was acquired via the digital Scopus database (www.scopus.com). Scopus was used due its large database of abstracts and citations of peer-reviewed literature, the inclusion of major medical journals and the inclusion of the five largest patent offices worldwide [68]. Scientific literature has been retrieved from May until September 2014. Search terms included: (metastatic) prostate cancer; mCRPC; circulating tumor cells; CTC; CTC trap; Circulating Tumor Cells therapeutic aphaeresis; therapy monitoring; management; medical technology; health technology assessment; economic evaluation, markov, steady state, transition, time-dependency, cyclic markov, hidden markov, continueous markov, markov trace AND/OR combinations have been used to select relevant articles. Besides language (English), no other filters were applied. Additional literature was found by 'snowballing' from found articles.

2.2. Clinical pathway

In order to see where the CTC trap could be of (most) clinical benefit, the clinical pathway was constructed. The clinical pathway flowchart was constructed using the National Institute of Clinical Excellence (NICE) prostate cancer guideline and the Guidelines on Prostate cancer of the European Association of Urology (EAU) [25], [26]. The pathway will help to identify possible implementation options for the CTC-trap. Literature, the clinical pathway and expert opinions [3] determined which implementation possibility for CTC trap was most plausible and favorable to study in this study.

2.3. Decision model

Most ideal, a clinical trial is performed to generate evidence in the evaluations of clinical interventions, pharmaceuticals, medical technology and healthcare programs. However, in case of lack of data and evidence, analytical models are used [69]. In healthcare, modeling is often used to inform decision making and supports clinical evidence since it allows decision analysis under uncertainty [70]. This study is using a State-Transition Model (STM). More specifically using a Markov cohort simulation model, due to its ability to reflect time (e.g., recurrence probability, time to event) instead of more static models like decision trees [69], [71]. This is due to the expected advantage of the CTC-trap in time. Other early-HTA methods like Bayesian method, Value of Information or micro simulation like Monte Carlo are not applicable due to the need of specific data, currently not available in this stage of the development of CTC-trap [72]. Examples of these specific data are large sample health outcomes from the different drugs RCT's, datasets from all patients characteristics and follow-up information.

2.4. Inputs

The model will be populated with data from existing sources and basic (optimistic) assumptions. The primary outcomes are

[3] Prof. L.W.M.M. Terstappen, MD, PhD and G. Attard, MD, MRCP, PhD where consulted as where supervisors Prof. M.J. IJzerman, PhD and Prof. S. Siesling, PhD.

costs and survival with a cycle length of 1 month. The cohort size was determined to be 2,100 patients, the proportion of yearly mCRPC incidence in the Netherlands.

2.5. Threshold analysis

With the results from the Markov analysis, a threshold analysis will determine the potential (incremental) health economic benefit for the CTC-trap in the clinical setting analysis with the Markov model [72]. These results will inform developers, payers and users with early development and strategic information.

3. RESULTS

The literature study was used to obtain thorough understanding and was used as fundament in Chapter 1.

3.1. Clinical pathway

Figure 3 shows the overall clinical pathway of prostate cancer based on the National Institute of Clinical Excellence (NICE) prostate cancer guideline and the Guidelines on Prostate cancer of the European Association of Urology (EAU) [25], [26]. The later is the golden standard in clinical practice in the Netherlands.

3.2. Implementation possibilities

With the information of the clinical pathway, possible implementation points of the CTC-trap devices were identified. An implementation possibility is defined as a point in the clinical pathway of prostate cancer where the implementation of the CTC-trap medical device is possible. The implementation possibility points are:

a) Using the CTC-trap device as pre-diagnose 'screening' device instead of the current used PSA screening. Screening is a successful approach to early detect PCa cases and increases the success in treatment [73]. By screening patients on CTC's, primary tumor patients could be identified.
b) Using CTC-trap as prognostic device and first-line therapy selection. With the information of the liquid biopsy, CTC-trap can give specific information for the prognoses of a PCa patient [74].
c) Using the CTC-trap as therapy management device in mCRPC patients. Current therapy response for mCRPC patients is monitored with image modalities (e.g., CT, MRI, PET or combination of aforementioned).

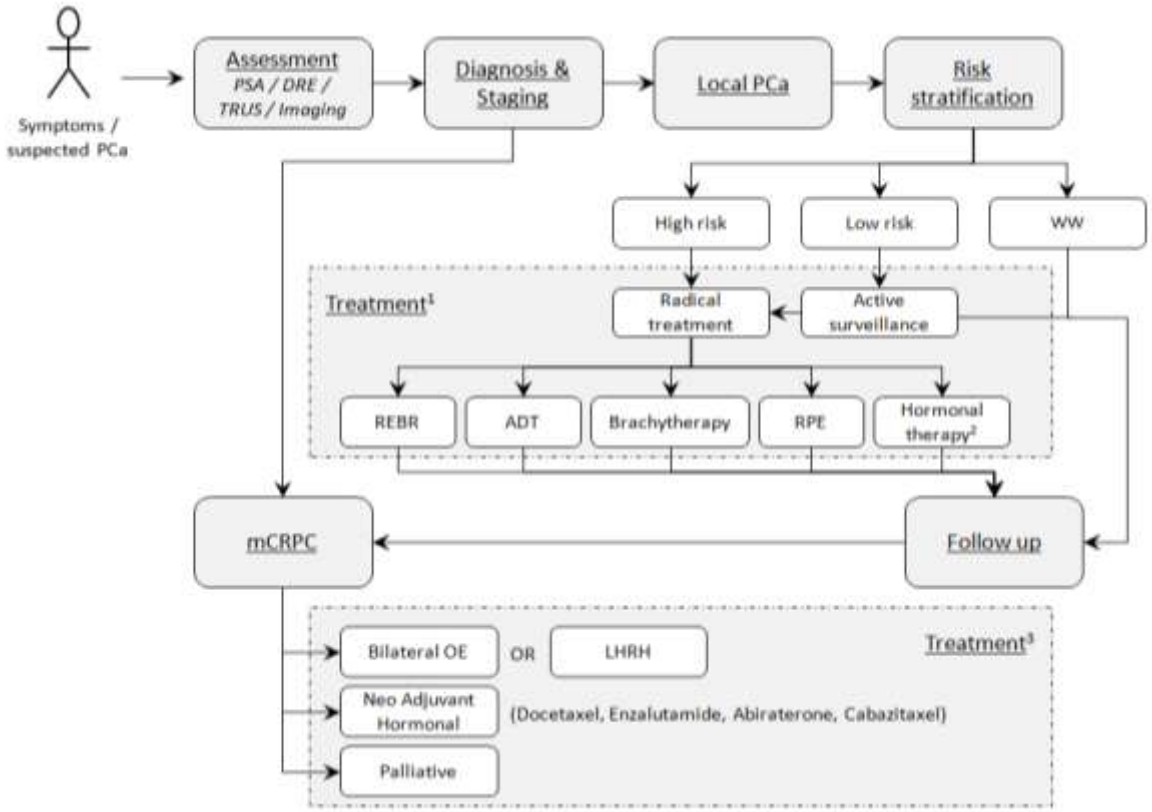

Figure 3. Flow chart clinical pathway, adopted from NICE and EAU guidelines [25], [26]. *[1] = First line treatment, mostly combination of therapies. [2] = First-line hormonal treatment, no neo adjuvant setting. [3] = Depending per patient and up to multidisciplinary team of clinicians. PSA = prostate specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound biopsy; PCa = prostate cancer; WW = Watchful Waiting; REBR = radical external beam radiation; ADT = androgen deprivation therapy; RPE = radical prostatectomy; OE = orchidectomy; LHRH = luteinizing hormone-releasing hormone*

However, they lack timely and sensitive early therapy response detection [75]. CTC trap could substitute the image modalities.

3.2.1. Screening

The screening option (Option A) is currently done by using the PSA level in blood. Even though PSA testing is controversial due to possible overdiagnosis [76], [77] and alternatives like serum surface-enhanced spectroscopy [78] already exist, it is not likely that CTC-trap screening will replace PSA. This is due to the favorable costs connected to a PSA lab test (EUR 9.82 in the Netherlands [79]) and time it takes a patient to give some blood. Since CTC-trap needs to filter 5 liter blood via apherase, it is already more time consuming ant the costs connected to staff would exceed the costs of a PSA lab.

3.2.2. Prognose

The second option, the CTC-trap as prognostic device (Option B) could be viable. Since an association between the clinical staging outcomes and the presence of CTC's in the blood is already established [48], [56], CTC-trap could be of value in the early staging of PCa. However, the applicability for prostate cancer is assessed as not probable in this stage of the development by expert opinion[4]. This was based upon the current clinical practice, the development of CTC-trap on this specific therapeutic area and the lack of clinical data.

3.2.3.Therapy management mCRPC

In option C, the current therapy response to neo adjuvant therapies for mCRPC patients is monitored with image modalities (e.g., CT, MRI, PET or a combination of the aforementioned) [26], [80], [81]. However they lack timely and sensitive early therapy response detection [75]. Assuming the current research hurdles in optimizing the technology are taken, CTC-trap could have a major clinical impact in targeted drug therapies response measurement as already shown in breast cancer [82], [83]. If a parallel is drawn in mCRPC [42], [53], CTC-trap could assess and detect the therapy response earlier in the process and hence it could save valuable time for the patient, counteract side effects of the drugs rapidly and prevent unnecessary costs of the neo adjuvant drugs.

3.3.Model structure

After deliberation, a conscious decision was made to construct a simple decision tree followed by two simulations runs of State-Transition model, in specific a Markov Cohort simulation model (shown in figure 4). One model run would incorporate the CTC-trap inputs and another model the current practice. This in contrary to a full decision tree, because of the characteristics of the clinical state patients go through when entering the mCRPC phase of the clinical pathway. Here, the patients receive a drug therapy, either respond to it and thus (temporarily) cease the disease progression or progress further. This can happen to any of the available drugs used to treat mCRPC patients. Building this in a decision tree would cause serial following of chance nodes and decision nodes each drug change, hence making it improbable to calculate solid outcomes.

The CTC-trap could detect therapy response in a time frame of three to five

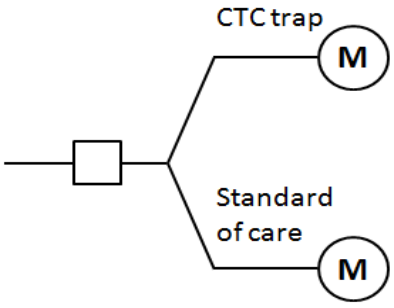

Figure 4. Schematic overview of the constructed decision tree and State-Transition Markov cohort simulation model(s) ('M').

[4] Experts as stated in Chapter 2.

weeks after start of the therapy [84]. This in contrast with the current standard, which is done by a bone scan to determine bone metastases, the most prevalent metastasis of PCa. The bone scan can be done after three to six months [80], [81]. This time difference is the most clinical relevant point of reference in the assumed cost-effectiveness the CTC-trap could bring into the clinical pathway [82]. Therefore, the current standard simulation would only have transitions at T=1, T=5, T=9, T=13, T=17 and T=21 since those are the moments clinical outcomes are measured and acted upon in the clinical setting. A basic assumption was made to keep the transition probabilities zero in the interstitial cycles. Cancelling the therapy at an earlier stage by using the CTC-trap in case of disease progression and non-response to the therapy, could save two up to four months of expensive drug- and therapy costs. See figure 5 for a visualization with an example of a CTC-trap and a scan at five months.

3.3.1.Parameter inputs

The cost and (dis-)utility parameters used as inputs in the model are shown in table 1 [85]–[92].

3.3.2 First model

To construct a working probabilistic model, several approaches have been used. The first model structure is shown in figure 6. It was based on the assumption of response and non-response to the drugs Docetaxel (Taxotere), the first choice of drugs and Abiraterone (Zytiga) -a second choice drugs in the mCRPC phase [26], [80]. The palliative state and death state were regarded and assumed to be non-essential in the expected difference of CTC-trap versus current therapy management practice [5]. In the model the progression/ stable definition was difficult to define; i.e. when after CTC-trap measurement or

Tabel 1. Parameter inputs overview

Tabel 1. Parameter inputs overview

Parameter description:	Value:	Source:
Costs		
Docetaxel drug cost 1 cycle	1178.43	Zorginstituut Nederland (2014)
Monthly indirect disease cost	34.17	Sangar, et.al. (2005)
Monthly indirect costs	56.49	NICE (2014)
Hopital DBC mCRPC guidance and admission (montly rate)	95.12	DBC Onderhoud (2014)
Total costs docetaxel (EUR)	*1364.21*	
Abiraterone drug cost 1 cycle	3498.00	Zorginstituut Nederland, 2014
Monthly indirect disease cost	34.17	Sangar, et.al. (2005)
Monthly indirect costs	56.49	NICE (2014)
Hopital DBC mCRPC guidance and admission (montly rate)	95.12	DBC Onderhoud (2014)
Total costs Abiraterone (EUR)	*3683.78*	
Costs CTC-trap blood analysis	0.00	
Costs current response analysis	2434.83	DBC Onderhoud (2014)
Utilities		
Utility mCRPC baseline	0.635	Sullivan, et.al. (2007)
Disutility adverse effects Abiraterone	0.255	Swinburn, et.al. (2010)
Disutility adverse effects Docetaxel	0.198	Dagher, et. al. (2004)
PFS Docetaxel (months)	2.4	Collins, et.al. (2007)
PFS Abiraterone after Docetaxel (months)	5.6	Zhong, et.al. (2012)
OS mCRPC (months)	18.2	

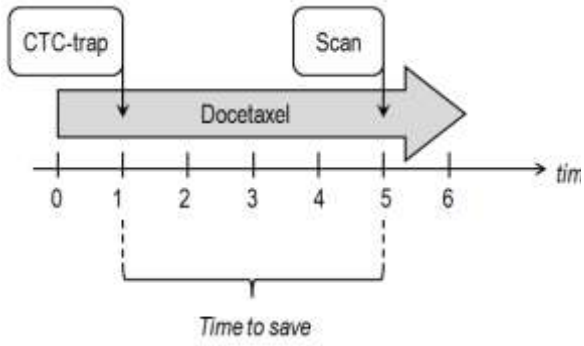

Figure 5. Visualization of the possible time to save using CTC-trap compared to current standard of assessing drug response and disease progression (time in months).

current standard patient review, the begin and end of a cycle could not be defined. With the PFS and OS, the transition probabilities where modeled and remodeled until the Markov trace appeared to be realistic in comparison to the results from clinical trials [85], [88], [93]–[96]). However, after first problem the definition of different

[5] Expert opinion elicitation as previous mentioned in Chapter 2.

states, the second arising problem was the memoryless characteristic of the Markov cohort model, also known as the Markov assumption, was clouding simple transition matrix building.

3.3.3. Second model

A second structure was tried, based on a simple three-states model as described in chapter two and three of Briggs, Claxton & Sculpher (2006)[69] as shown in figure 7. This Markov cohort model structure resulted in the reappearance of the first identified problem when constructing the transition matrix. The direct result was a decrease of initial patients (input of 2100, minus 105 to 207 in T=5 and T=9) followed by an increase in patients (plus 238 in T=13 and 372 in t=17) over the time in the current standard simulation. Here, the Markov assumption showed the inability of following the patients in the transitions. It could not distinguish

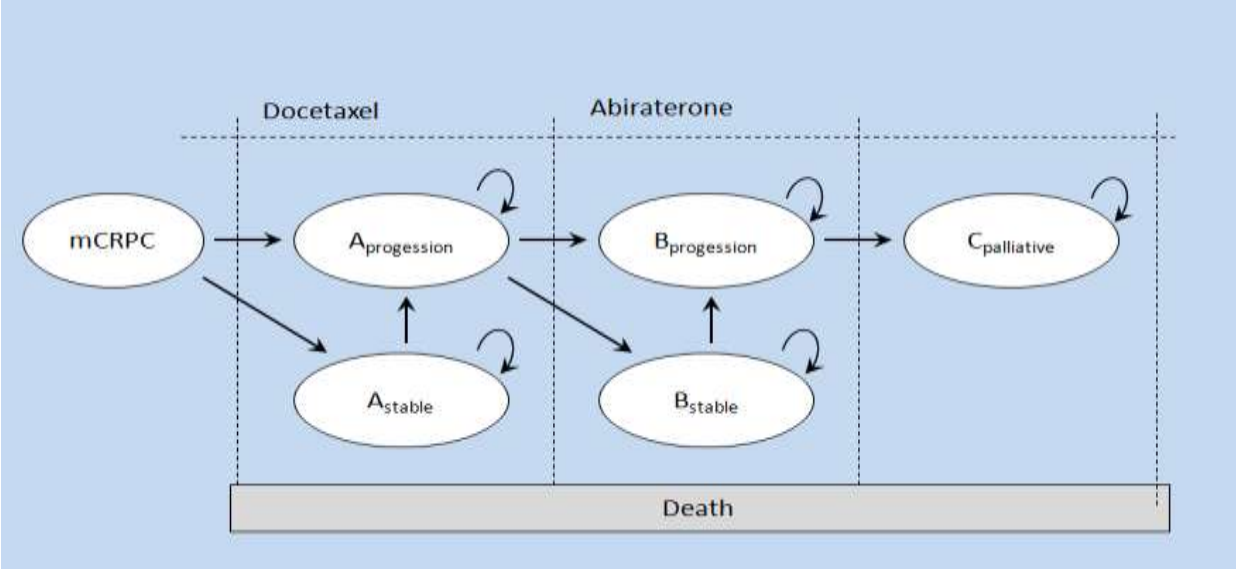

Figure 6. Markov cohort model first version. $A_{progression}$ contains the patients who have disease progression despite the Docetaxel drug treatment; A_{stable} contains the patients who respond to the Docetaxel drug treatment. $B_{progression}$ contains the patients who have disease progression despite the Abiraterone drug treatment; B_{stable} contains the patients who respond to the Abiraterone drug treatment. $C_{palliative}$ are patients who continue to receive palliative treatment (not further defined or examined).

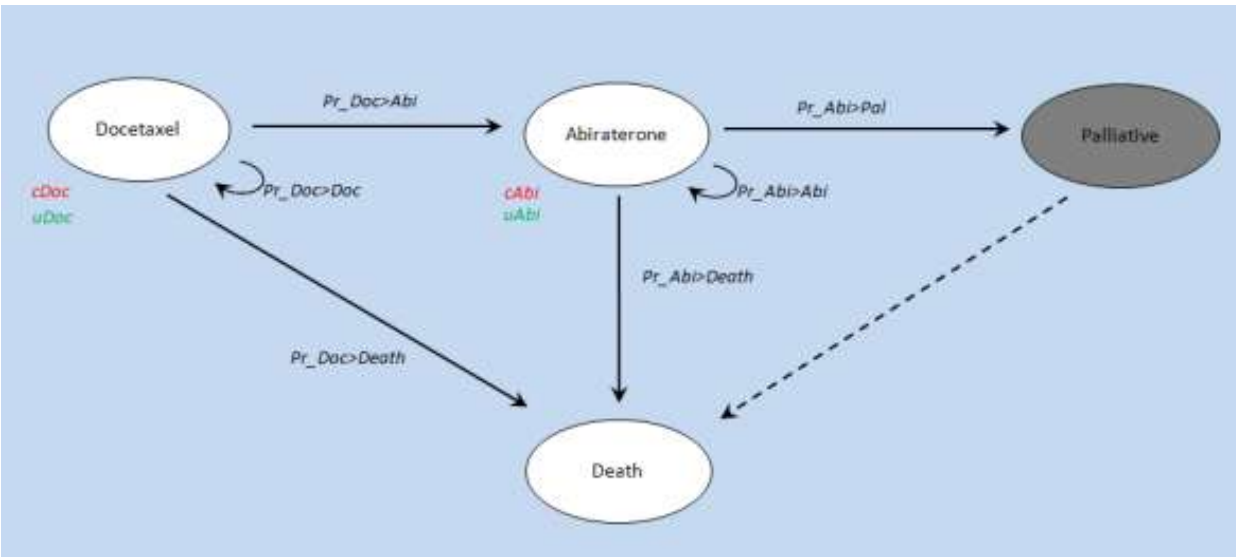

Figure 7. Markov cohort model second version based upon the Three-state model used in Briggs, Claxton & Sculpher, 2006 [69]. Docetaxel state contains the patients who have good response to the Docetaxel drug treatment and thus keep receiving the drug Abiraterone state contains the patients responding to the Abiraterone drug. Palliative state holds patients who continue to receive palliative treatment (not further defined or examined).

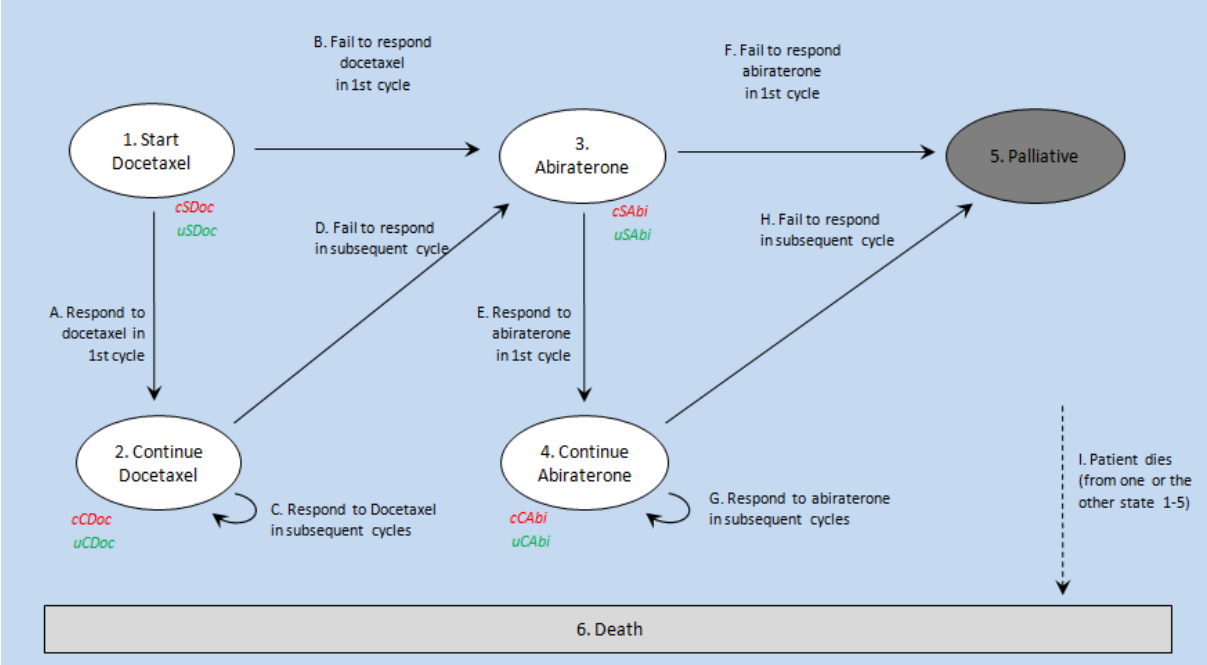

Figure 8. Markov cohort model third version. Start Docetaxel drug treatment with transitions to either response in first cycle or fail to response. Continue the Docetaxel with transitions in subsequent cycles if fail in therapy is detected. Same structure for Abiraterone. Palliative and death are same in earlier structures.

between already treated patients and still responding patients in a same state and the different transition probabilities that should be assigned to the corresponding patient groups. The different groups should be allocated different transition probabilities based upon the history of the patient. For example, a patient who has a good response to Docetaxel and stays in the Docetaxel state for a couple of months, has per definition a different transition probability for progression and non-response to the drug in comparison to a patients who does not respond in the first cycle. So assuming that the individual patients history determines the transaction probabilities rates to a next state, makes the fixed transition probability matrix unmanageable.

3.3.4. Third model

Ultimately, a third probabilistic model was constructed based upon response to the drugs in two states with state-subsequent transition probabilities. The overall model structure is displayed in figure 8. This model has successfully been used in cost-effective assessment of new pharmaceutical therapies for epilepsy in adults [97]. It reflects the difference in a direct non-response to a drug therapy and an initial response with subsequent failure to response in effect over time. After construction of the model and applying the earlier modeled and assumed transitions matrix to the new structure, the big disadvantage of deterministic cohort models(re-)appeared. Hawkins et.al. relied on patient-level data and R-programmed probabilistic model. In the mCRPC study, patient level data is not yet available due to the pre-clinical state of the CTC-trap making it thus deterministic and only applicable on cohort model simulation. To overcome this barrier, the model was subjected to several attempts to implement time dependency [97].

3.4. Time dependency

Time dependency is being used to reflect real life situations more closely in simplified modeling in HTA decision analysis. This is to overcome potentially misleading results were for instance, an assumed fixed transition is considered too strong 9with high uncertainty), and henceforth outcomes are off .

3.4.1.Model-time varied transition probability

First, probabilities have been varied according to the time in the state. So if a patients leaves Start Docataxel state (sDoc) to Continue Docetaxel (cDoc) at t=1, a probability corresponding the tp_sDoc-$cDoc_{(t=1)}$ was generated. This could be done for the start states of Docetaxel and Abiraterone, creating a 3D transition probability matrix with varying transition probabilities for tp_sDoc-cDoc and tp_sAbi-cAbi. However, this could work for these transitions, but should also be incorporated in the transitions cDoc to the start of Abiraterone in case it fails to respond in a subsequent cycle. The same would apply for the transition between Continue Abiraterone to Palliative and even from all the states to the death state, depending on the time spend in the model and the previous (t-1) state. So initially it worked for the t=0 until t=2, though after t=2 the memorylessness of the Markov model would not allow to follow the cohort or fractions of the cohort passed the Continue Docetaxel and the Start Abiraterone state (e.g. patients can reach that state at any t=>2). And without Monte Carlo simulation or R-simulation, the cohort model cannot trace the fractions of patients at any t to enter or leave a certain state.

Survival models could be used to determine the varying transition from state to state (by altering the rates into transition probabilities by applying either a Weibull regression or simple exponential regression $f(t)=\lambda exp^{\{-\lambda t\}}$ and $tp(t_u)=1-exp^{\{-\lambda u\}}$ [69]. However, this can not be done without the specific rough data input from a longitudinal study concerning the patient characteristics. And more importantly, only if the model can establish entry and exit points of patients (or fraction of cohorts) per state. In the case of the mCRPC, this cannot be applied in the CTC-trap model.

3.4.2. Tunnel states

Briggs, Claxton & Sculpher (2006)[69] and also others in literature [98], [99] speak of the possibility to built so called 'tunnel states' into the cohort model to relax the Markov assumption and reflect time into the model. The building of tunnel states into the CTC-trap mCRPC would imply splitting the cDoc and cAbi states into 5 separate tunnel states. This led to a model with 78 different tunnel states routings as shown in figure 9. With

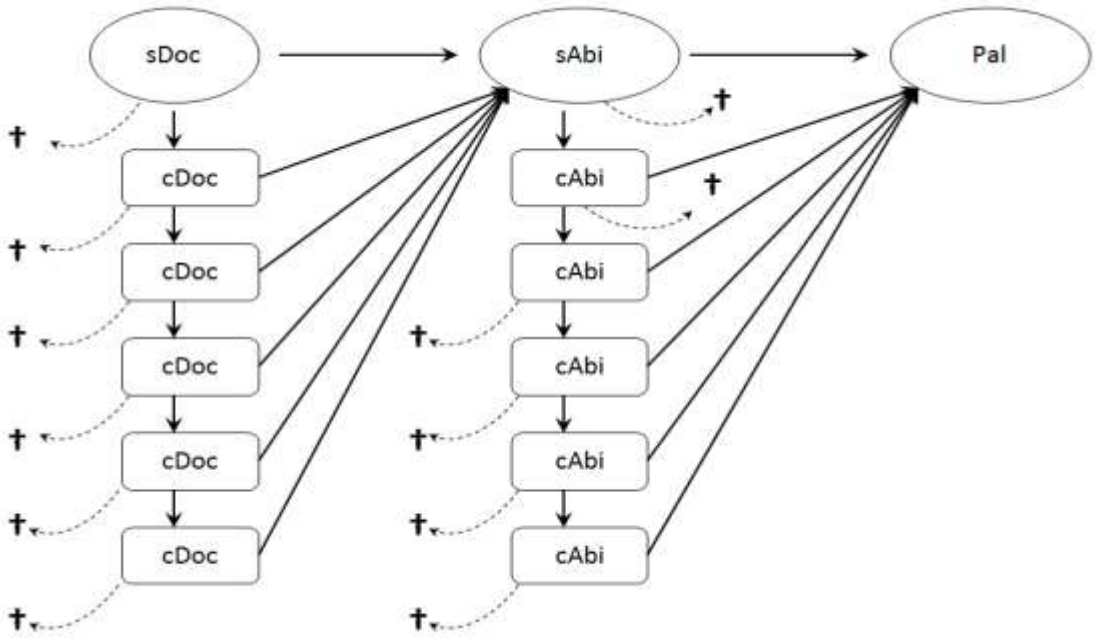

Figure 9. Tunnel states routing map for the mCRPC case study. (sDoc=starting Docetaxel treatment; cDoc=continue Docetaxel treatment; sAbi=starting Abiraterone treatment; cAbi=continue Abiraterone treatment' Pal=palliative care; †=death.)

the limited transition probability data, it was not feasible to create 78 different transition probability routes and apply the cohort simulation resulting in a workable Markov trace. This was due to the sAbi state which could not link the different routes with entry and exit probabilities (e.g. patients from different routes coming into the state, and leaving the state towards the next states). As described in earlier paragraphs as main problem; the memoryless trait in the cohort approach.

3.4.3. R-software

Hawkins et. al. describe a R code that could be implemented to simulate a same decision problem like the CTC-trap mCRPC case [97]. The epilepsy study Hawkins et. al. used, shows resemblance with the problems this mCRPC case is dealing with. Starting of with a steady state Markov model, with similar construction of response to therapy and failure to respond to therapy and subsequent states. The described R code however, is given partially and in other publications the code is not sufficient to reproduce for this mCRPC case [97], [100]. Hence, validation of the used R code to overcome Markov model limitations in the mCRPC case was not possible.

3.4.4. Cohort scenarios

Finally, cohort scenario simulations with three different scenario's were tried to construct using the third model (figure 8). The presumed scenarios were:

a. Short time of successful therapy response (S1): with a 1 month PFS therapy response to all subsequent therapies.
b. Average time of successful therapy response (S2): with a 3 month PFS therapy response to all subsequent therapies.
c. Long time of successful therapy response (S3): with a 5 month PFS therapy response to all subsequent therapies.

In these scenario's the following baseline assumptions were used: positive therapy response in 60% of the patients, 40% overall direct mortality (representing the non-responsive group of patients [29]). After running the scenario's it became apparent that the PSF of 1, 3 or 5 months does not show differences, since the current therapy monitoring practice is set at t=5 months as cycle length and, thus, shows no differences compared to the S1 to S3 scenario's.

4. CONCLUSION & DISCUSSION

This study identified different Markov modeling approaches for early modeling of CTC-trap in mCRPC. There seems to be an indication that CTC-trap is a probable technology to use in the diagnostic pathway of prostate cancer. Like the consulted experts already argued, especially in the mCRPC state where the CTC's are in abundance, and hence the CTC-trap could function optimal. When looking at the inputs on an individual level, a basic calculation based on a quick-and-dirty method shows a time frame opportunity and thus monthly costs to spare when patients do not respond to treatments caught in an early time frame by CTC-trap (i.e. Docetaxel treatment cost cuts of 3 months saves 4,092.63 euro per patient and, on top of that, the adverse effects the treatment brings along and the assumed quality of life gained or sustained).

Two main problems were identified selecting these models, firstly, the time-dependency in transition probabilities and, secondly, the available patient level data to populate the models in early HTA.

4.1. Time-dependency in transition probabilities

The intended study method - a STM Markov cohort model - is an often applied health economic method to study cost-effectiveness [71], [101], [102]. Markov models are very widely used and applicable to a range of problems, yet the main problem is to deal with time relations as Markov is memoryless. The time-dependency in treatment sequences cases (often used in personalized medicine), like the mCRPC case, makes a cohort model without patient-level data not easy to apply. Like Shah et.al. in 2012 describe, the memoryless feature of the Markov model is a limiting factor when transition probabilities are time-dependent in subsequent transition and, hence, not constant [99]. A possible solution is a Tunnel state, also described by Briggs, Claxton & Sculpher [69]. However, in a treatment sequence like in the mCRPC case, often used in personalized medicine, the conditional transition - as defined by a failure to response to therapy before continuing to a new therapy regime - makes a cohort model (too) difficult to build. Besides tunnel states, other solutions exist like 'rarefying' the model into a basic model (e.g. the second model in this study – figure 7) with a minimum of states in order to limit the transitions probabilities. This, however, does not seem to work either, since the conditional transition and time-dependency can hardly be expressed in a rarified cohort model. This is supported by the Ceteris Paribus argument; when complexity increases, e.g. in diagnostic pathways and guidelines when introducing time-dependency, the uncertainty increases in decision modeling [66]. Thus, constructing straightforward transition probabilities proofs to be rather difficult.

4.2. Patient level data requirements

The second problem is that patient-level data is required to successfully model a STM. In the cohort model approaches in this study, a repeated problem occurred on the lack of patient specific date due to the multi-plural combination of treatments and their responses to the different treatments. General population data could not be used to accurately generate these patients-treatments responses characteristics and inputs. This results an assumption-based approach, which leads to a great uncertainty. Subsequently, this uncertainty could not be run in a sensitivity analysis due to the missing data resulting in a fault Markov trace. When patient level data is available, a STM Monte Carlo simulation could be used to attain a solid decision model. Since Monte Carlo would allow for structured sensitivity analysis to overcome the uncertainty problem [66].

4.3. Applicability of Markov models in Personalized Medicine

An relevant point of discussion, is the usability of straight-forward (cohort) Markov models in the current medical practice. If taken into account that - especially in cancer treatments - the personalized medicine is becoming more and more evidence-based, diagnostic pathways will not be singular sequences, but a multi-plural combination of treatments sequences. Are the traditional cost-effectiveness studies, comparing a single new treatment to a golden standard, still appropriate in the current medical practice?

Again, patient level information is required to reflect these conditions. This data availability requirement looks like the main condition to have a (method-)beneficial working Markov models. By developing new models for a new device or technology innovation, it may be difficult to obtain data that fully considers stratification of patients by risk or past interventions, or to consider the full range of outcomes in a clinical pathway [66], [103]. When letting go of the Markov approach, another possible method could be the more complicated Discrete Event Simulation. DES enables a larger flexibility to reflect disease progression over time and thus include the time-dependency and conditional transition from different disease states. Earlier research already establish the validity of DES and Markov in HEA [104]. Given the condition that the patient-level data requirement is met, a DES could give the results the CTC-trap consortium is looking for in the development of the CTC as non-invasive cost-effective diagnostic and treatment monitoring device.

The simplifications applied in health economic assessments cause major uncertainty and, especially in personalized medicine, may lead to large variations in outcomes. The (simple) health economic modeling approaches are rapidly introduced, applied and validated to be used for reimbursement and regulatory purposes in many different countries. However, for personalized medicine, HEA might require different approaches to substantiate adequate outcomes [65], [66], [105], [106].

4.4. Limitations

The main limitation of the study is the lacking of patient-level inputs to simulate a proper decision model. Clinical trials data alone only provide limited data on efficacy of a single drug compared to current treatment standards. It does not explore different treatment sequences which would allow conditional and time-dependent data to be used in health economic decision modeling.

4.5. Recommendations

When looking at the results of this study and the existing literature on methodological issues in economic assessments of cancer care and personalized medicine, it is recommended to investigate and explore other modeling approaches. As previous mentioned, DES or a new approach called 'timed Markov automation' could be explored. Timed Markov automation is an approach used in informatics and mathematical science and is expected to be of added-value in health economic decision modeling [107], [108].

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Wander Kenter, June 2015

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APPENDIX

I. List of figures and tables

II. Markov trace van de runs

(Next pages)

Markov trace basic calculations. Probabilistic Markov Model, third generation with average successful therapy scenario (S2) and correction.

	CTC trap									Current standard								
Time	**sDoc**	**cDoc**	**sAbi**	**cAbi**	**pal**	**death**	**check**	**Costs**	**DC Costs**	**sDoc**	**cDoc**	**sAbi**	**cAbi**	**pal**	**death**	**check**	**Costs**	**DC Costs**
0	2100						2100	2,666,148.80	2,666,148.80	2100						2100	2,666,148.80	2,666,148.80
1	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
2	5	1024	574	332	67	98	2100	4,553,511.80	4,250,751.99	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
3		618	361	653	272	196	2100	4,417,678.70	3,984,493.08	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
4		371	217	677	546	289	2100	3,675,148.09	3,202,679.24	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
5		222	130	578	791	378	2100	2,820,314.90	2,374,629.47	5	1024	574	332	67	98	2100	4,553,511.80	3,833,934.75
6		133	78	450	976	462	2100	2,061,325.07	1,676,889.28	5	1024	574	332	67	98	2100	4,553,511.80	3,833,934.75
7		80	47	332	1099	542	2100	1,458,276.72	1,146,192.32	5	1024	574	332	67	98	2100	4,553,511.80	3,833,934.75
8		48	28	236	1169	619	2100	1,007,855.04	765,376.77	5	1024	574	332	67	98	2100	4,553,511.80	3,833,934.75
9		29	17	164	1199	691	2100	684,446.43	502,199.54		618	361	653	272	196	2100	4,417,678.70	3,241,387.69
10		17	10	112	1200	760	2100	458,507.90	325,044.88		618	361	653	272	196	2100	4,417,678.70	3,241,387.69
11		10	6	75	1182	826	2100	303,808.77	208,092.51		618	361	653	272	196	2100	4,417,678.70	3,241,387.69
12		6	4	50	1152	888	2100	199,507.68	132,030.85		618	361	653	272	196	2100	4,417,678.70	3,241,387.69
13		4	2	33	1113	948	2100	130,038.05	83,146.87		371	217	677	546	289	2100	3,675,148.09	2,349,904.95
14		2	1	21	1071	1004	2100	84,222.90	52,031.38		371	217	677	546	289	2100	3,675,148.09	2,349,904.95
15		1	1	14	1026	1058	2100	54,253.78	32,383.57		371	217	677	546	289	2100	3,675,148.09	2,349,904.95
16		1	0	9	981	1109	2100	34,784.29	20,060.31		371	217	677	546	289	2100	3,675,148.09	2,349,904.95
17		0	0	6	936	1157	2100	22,209.79	12,375.38		222	130	578	791	378	2100	2,820,314.90	1,571,490.12
18		0	0	4	892	1203	2100	14,129.40	7,606.72		222	130	578	791	378	2100	2,820,314.90	1,571,490.12
19		0	0	2	850	1247	2100	8,959.76	4,660.47		222	130	578	791	378	2100	2,820,314.90	1,571,490.12
20		0	0	1	809	1289	2100	5,665.13	2,847.10		222	130	578	791	378	2100	2,820,314.90	1,571,490.12
21		0	0	1	770	1329	2100	3,572.64	1,734.77		133	78	450	976	462	2100	2,061,325.07	1,000,919.48
22		0	0	1	732	1367	2100	2,247.72	1,054.52		80	47	332	1099	542	2100	2,061,325.07	1,000,919.48
23		0	0	0	697	1402	2100	1,411.11	639.64		48	28	236	1169	619	2100	2,061,325.07	1,000,919.48
24		0	0	0	663	1437	2100	884.16	387.22		29	17	164	1199	691	2100	2,061,325.07	1,000,919.48
Total								28,307,177.69	24,968,692.46								87,331,139.24	64,717,639.92

Markov trace basic calculations. Probabilistic Markov Model, third generation without scenario or correction.

	CTC trap									Current standard								
Time	**sDoc**	**cDoc**	**sAbi**	**cAbi**	**pal**	**death**	**check**	**Costs**	**DC Costs**	**sDoc**	**cDoc**	**sAbi**	**cAbi**	**pal**	**death**	**check**	**Costs**	**DC Costs**
0	2100						2100	2,666,148.80	2,666,148.80	2100						2100	2,666,148.80	2,666,148.80
1	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
2	5	1040	574	331	67	98	2115	4,570,497.22	4,266,608.06	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
3		638	366	635	275	196	2110	4,397,454.39	3,966,251.91	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
4		389	224	638	557	290	2098	3,583,521.54	3,122,831.99	105	1575	420	0	0	0	2100	3,638,269.04	3,515,235.79
5		237	137	527	817	379	2098	2,682,157.86	2,258,304.94	5	1040	574	331	67	98	2115	4,570,497.22	3,848,236.02
6		145	83	398	1025	463	2114	1,909,032.26	1,552,998.97	5	1040	574	331	67	98	2115	4,570,497.22	3,848,236.02
7		88	51	285	1179	544	2147	1,314,613.46	1,033,274.29	5	1040	574	331	67	98	2115	4,570,497.22	3,848,236.02
8		54	31	197	1288	622	2192	884,471.29	671,677.72	5	1040	574	331	67	98	2115	4,570,497.22	3,848,236.02
9		33	19	133	1364	699	2247	584,933.88	429,184.10		638	366	635	275	196	2110	4,397,454.39	3,226,548.48
10		20	12	88	1415	775	2309	381,783.18	270,653.28		638	366	635	275	196	2110	4,397,454.39	3,226,548.48
11		12	7	57	1449	850	2376	246,623.18	168,923.49		638	366	635	275	196	2110	4,397,454.39	3,226,548.48
12		7	4	37	1471	925	2445	157,994.63	104,558.20		638	366	635	275	196	2110	4,397,454.39	3,226,548.48
13		5	3	24	1487	1000	2517	100,531.69	64,280.38		389	224	638	557	290	2098	3,583,521.54	2,291,318.55
14		3	2	15	1497	1074	2590	63,609.56	39,296.83		389	224	638	557	290	2098	3,583,521.54	2,291,318.55
15		2	1	10	1504	1148	2664	40,058.71	23,910.67		389	224	638	557	290	2098	3,583,521.54	2,291,318.55
16		1	1	6	1509	1223	2739	25,127.10	14,490.95		389	224	638	557	290	2098	3,583,521.54	2,291,318.55
17		1	0	4	1513	1297	2814	15,707.74	8,752.41		237	137	527	817	379	2098	2,682,157.86	1,494,508.50
18		0	0	2	1516	1371	2890	9,790.83	5,271.00		237	137	527	817	379	2098	2,682,157.86	1,494,508.50
19		0	0	1	1518	1446	2965	6,087.42	3,166.41		237	137	527	817	379	2098	2,682,157.86	1,494,508.50
20		0	0	1	1520	1520	3041	3,776.58	1,897.98		237	137	527	817	379	2098	2,682,157.86	1,494,508.50
21		0	0	1	1522	1595	3117	2,338.51	1,135.51		145	83	398	1025	463	2114	1,909,032.26	926,970.52
22		0	0	0	1524	1669	3193	1,445.62	678.22		88	51	285	1179	544	2147	1,909,032.26	926,970.52
23		0	0	0	1525	1744	3269	892.36	404.49		54	31	197	1288	622	2192	1,909,032.26	926,970.52
24		0	0	0	1527	1819	3346	550.12	240.93		33	19	133	1364	699	2247	1,909,032.26	926,970.52
Total								27,287,416.95	24,190,177.33								85,789,877.99	63,877,420.21