Value of Information Analysis for Diagnostic Test Evaluations

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Preface

The final part of the study program of Business Mathematics and Informatics (BMI) at the Vrije Universiteit in Amsterdam consists of an internship. I did my internship in the Assessment of Radiological Technology (ART) research group at the Department of Epidemiology and Biostatistics of the Erasmus Medical Center in Rotterdam.

I am glad that I may continue my work at the Erasmus MC. In August my PhD program will start.

I would like to thank Myriam Hunink for her help, guidance and the opportunity to do my internship at the Erasmus MC. Her book “Decision making in health and medicine” [4] gave me a good basis to start my internship. Also I would like to thank all members of the ART group: Jan-Jaap, Ineke, Majanka, Joke, Montiva, Lei-Man, Daphne, Edwin and all the others. Thanks to Nano who updated the Treeage Tro software for me almost every week. Also I would like to thank my supervisors at the Vrije Universiteit: Auke Pot and GJ Franx for their comments. Thanks to Ronald for improving my English. I owe you a bottle of ‘apfelkorn’! And last but not least thanks to Eva for her great support.

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Abstract

Choosing between different diagnostic test strategies is hard and commonly demonstrates only very small differences in costs and benefits. Furthermore, each strategy contains uncertainty (e.g. the real sensitivity and specificity of the test). Because of this uncertainty, there is a chance of not choosing the optimal strategy. This raises the question if more research is needed. With more research the uncertainty can be decreased and so can the chance of choosing the wrong strategy. But, on the other hand more research would cost a lot of money and is time consuming. The decision whether new diagnostic research studies are necessary therefore depends on a trade-off between the expected benefit and the costs of research.

In the internship the focus is on the benefits of doing more research with the objective to develop a general stochastic decision model for diagnostic tests. Through this model the "value of information" can be determined.

A model is built to model the whole process of testing, treatment and follow up. With the model the expected benefit (in QALYs) and costs (in euros) can be calculated for each set of model parameter values and for each diagnostic test strategy. The model parameters contain all uncertainties. They are not fixed but have an underlying distribution.

With more research the uncertainty of these model parameters can be decreased. The value of information (of this research) is the incremental benefit of the optimal strategy with additional information versus the optimal strategy without additional information. The expected benefit of eliminating all parameter uncertainties is called the expected value of prefect information (EVPI). The expected benefit of eliminating all parameter uncertainties for a set of model parameters is called the expected value of partial prefect information (EVPPI). The EVPI and EVPPI can be estimated by Monte Carlo simulation.

An Excel sheet is constructed to determine all strategies with their model parameters (including their distributions) and can perform the EVPI and EVPPI estimations.

The EVPI and EVPPI gives just an upper bound of the expected benefit of doing more research, because the elimination of all parameter uncertainty is impossible. Therefore the next step is to calculate the expected value of partial sampling information (EVPSI(n)). The EVPSI is the expected benefit of doing a research study with a sample size of n.

Contents

Abbreviations

ART	-	Assessment of Radiological Technology
CABG	-	Coronary Artery Bypass Graft
CAD	-	Coronary Artery Disease
CTA	-	Computed Tomography Angiography
EVPI	-	expected value of perfect information
EVPPI	-	expected value of partial perfect information
EVPSI	-	expected value of partial sampling information
FN	-	false-negative (test result)
FP	-	false-positive (test result)
NHB	-	net health benefit
NMB	-	net monetary benefit
QALY	-	quality-adjusted life years
TN	-	true-negative (test result)
TP	-	true-positive (test result)
VOI	-	value of information
WTP	-	willingness to pay

Definitions

sensitivity	-	the proportion of people with a positive test result who have the disease $\mathbb{P}(\text{positive test result}\vert\text{disease})$
specificity	-	the proportion of people with a negative test result who haven't got the disease $\mathbb{P}(\text{negative test result}\vert\text{no disease})$

1 Introduction

1.1 Erasmus Medical Center, Department of Epidemiology & Biostatistics

The Erasmus Medical Center is the largest university medical center in the Netherlands, with over 10,000 employees. The core activities of Erasmus MC are patient care, education and research. Every medical department has an educational purpose and also conducts scientific research. Erasmus MC's research covers the entire spectrum from fundamental non-clinical research to patient related research.

The Department of Epidemiology & Biostatistics offers research consultancy facilities for clinicians of the Erasmus Medical Center, Rotterdam in clinical epidemiology and biostatistics. The research activities of the department are organized in three clusters; Epidemiology of Diseases, Basic Epidemiology, Clinical Epidemiology.

The Assessment of Radiological Technology (ART program) is a joint effort of the division of Clinical Epidemiology and the department of Radiology. The ART program comprises a network of researchers who focus on the assessment of medical imaging technology, both diagnostic imaging and image-guided therapies, especially related to cardiovascular disease. The research performed is based on methods from clinical epidemiology, decision sciences, and medical technology assessment. Methodological research focuses on developing the methods and study design for evaluating diagnostic and therapeutic imaging procedures.

1.2 Problem description

Evaluating and comparing diagnostic test strategies entails a long process of clinical studies, data collection and decision modeling. At the end of this complex process the evaluation commonly demonstrates only very small benefits from replacing one diagnostic strategy with another, leading to the typical conclusion "more research is needed". But is more research really necessary, and are the associated research costs justified? If a new clinical study is undertaken to assess patient outcomes and costs related to diagnostic testing strategies, it will need to be extremely large to demonstrate a difference. Furthermore, by the time a complete assessment of the new diagnostic technology has been performed, the results are frequently a moot point: with the rapid advances in technology, either the new test has been implemented or it has been discarded in lieu of an even newer technique, which applies in particular to imaging tests.

These considerations call into question whether elaborate large diagnostic research studies are always necessary. More research is expected to have a benefit, since it usually decreases decision uncertainty and therefore the probability and harm of choosing the wrong diagnostic strategy. At the same time, research also has a financial cost and may result in harm because of forgone benefits from delaying adoption of beneficial interventions. The decision whether new diagnostic research studies are necessary therefore depends on a trade-off between the expected benefit and the costs of research. In this subproject the focus is on the expected benefit of doing more research.

1.3 Objectives

The focus is on the value of information (VOI) gained from the evaluation of diagnostic test strategies. VOI is a quantitative measure of the value of knowing the outcome of uncertain variables prior to making a decision. Each diagnostic test strategy has such uncertain variables. Short-term variables that will be included are:

- sensitivity and specificity of the test
- probability of uninterpretable test results
- impact on clinical practice
- health care cost of the test
- patient burden, time costs, friction costs, and other non-health care costs associated with undergoing the test

Long-term variables that will be included are quality adjusted life years (QALYs) and costs (health care and non-health care) associated with the test and treatment following:

- true positive test results
- false positive test results
- true negative test results
- false negative test results

The main objective is to develop a general stochastic decision model for diagnostic tests, with which the value of information can be determined, and that can be analyzed for various scenarios.

1.4 Further content

In section 2 a model will be given to evaluate and compare different diagnostic test strategies. With the model we can calculate the expected benefit and costs. Section 3 describes the methods and algorithms for the value of information analysis. In section 4 we show how the value of information analysis is implemented and give a VOI example for two types of tests for patients with suspected coronary artery disease.

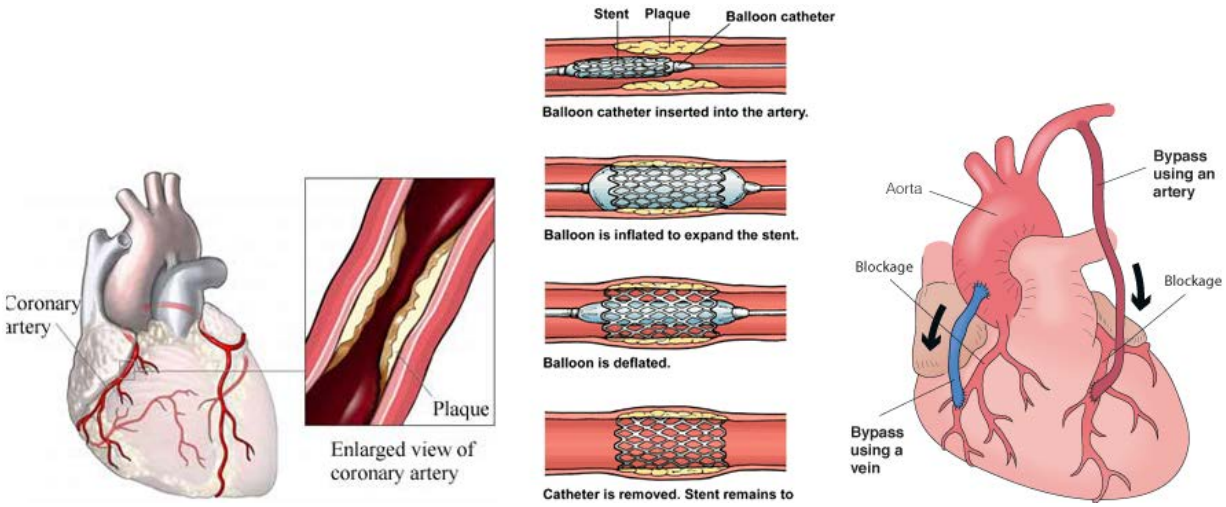

Figure 1: a) Coronary artery disease b) stent c) CABG

2 Model

2.1 General

To compare different diagnostic test-treatment strategies, we first model the whole process of testing, treatment and follow up. After deriving this model we can compare different test-treatment strategies. All strategies follow a similar process. Patients with the suspected disease, will get one or more tests. After surviving the test(s) (there is generally a negligible risk of dying from the test) the patients will be split in a positive and a negative group, depending on the result(s) of the test(s). The positive group gets a treatment P and the negative group gets an other treatment N. After surviving their treatment, patients are monitored for a fixed amount of time. We call this the follow-up period of a patient.

For example, for patients with suspected coronary artery disease (CAD), there can be chosen between two types of diagnostic tests, a coronary angiography or a computed tomography angiography (CTA). Coronary artery disease (CAD) occurs when the arteries that supply blood to the heart muscle (the coronary arteries) become hardened and narrowed due to plaque on their inner walls. Because of CAD the blood flow to the heart muscle is reduced and the heart muscle is not able to receive the amount of oxygen it needs. See figure 1a for a graphically illustration.

CAD is treated with a stent or a coronary artery bypass graft (CABG). With stenting, a balloon catheter with a stent is inserted into a blood vessel in the patients groin. When the tip of the catheter reaches the right location in the coronary artery, the balloon is slightly inflated to expand the stent and the artery. The stent stays permanently. See figure 1b for a graphically illustration. With a CABG a segment of a healthy blood vessel from another part of the body is used to make a detour around the blocked part of the coronary artery. See figure 1c for a graphically illustration.

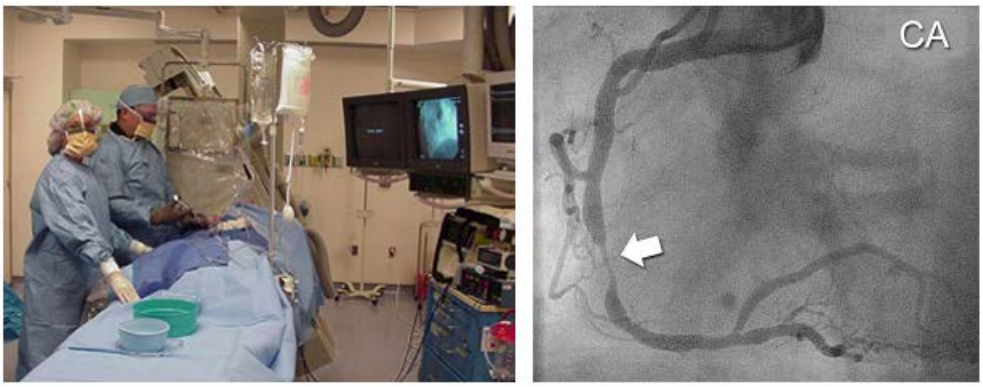

Figure 2: Coronary angiography

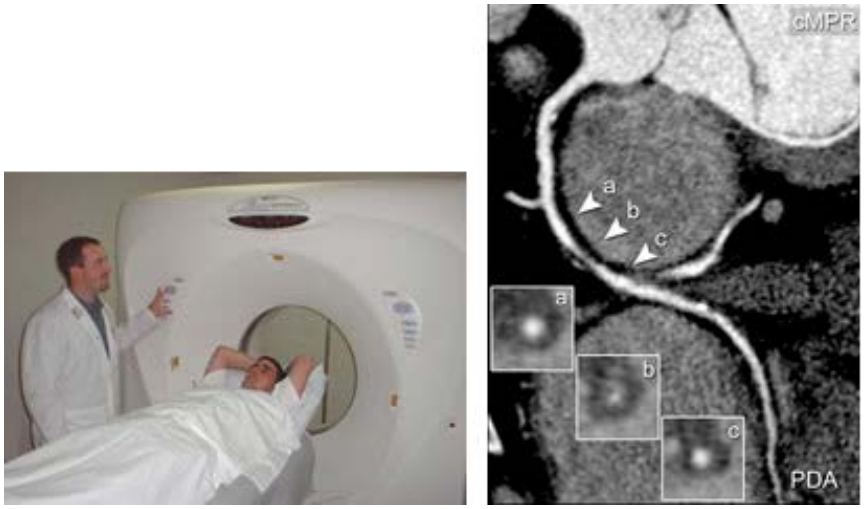

Figure 3: computed tomography angiography (CTA)

We distinguish two types of tests for diagnosing CAD. First coronary angiography which is the reference standard test, with an assumed reliability of 100%. With a coronary angiography a very small catheter is inserted into a blood vessel in the patients groin. The tip of the catheter will be positioned in the heart and will inject special contrast fluid. The fluid is visible by x-ray. See figure 2 for an illustration. Because a coronary angiography is expensive and invasive, it might be better to perform a cheaper and less invasive test (but is less reliable): computed tomography angiography (CTA). With a CTA first contrast fluid is injected in the patients arm. Then a CT scan is used to take x-rays. See figure 3 for an illustration.

General we distinguish the reference strategy, which is to perform the reference standard test, and other strategies with another test. In the reference strategy the reference standard test, with an assumed sensitivity and specificity of 1, is always performed (a coronary angiography in our example). The advantage of this strategy is that after the test all patients are categorized correctly and get the optimal treatment. There are not any false positive (FP) and false negative (FN) test

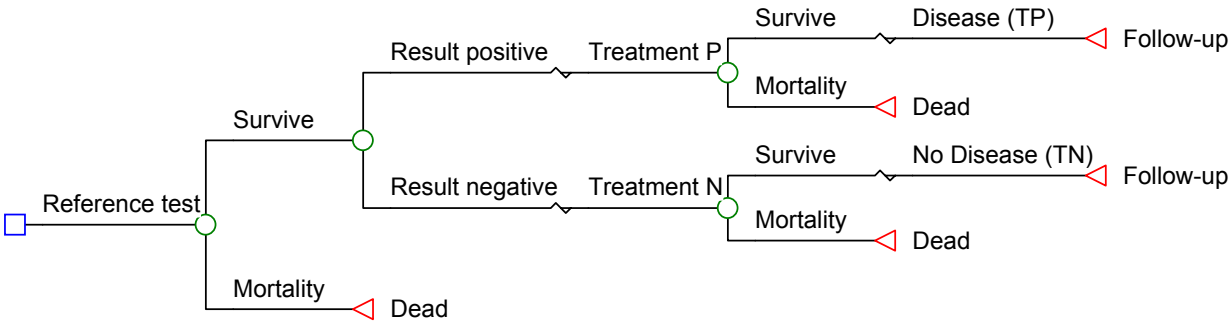

Figure 4: Reference test strategy

results, which could cause harm.[1] The disadvantages of this strategy is, that the reference test is generally more invasive, so it has a higher probability of morbidity (such as an allergic reaction) and mortality. Another disadvantage is that the reference test is often very expensive. A graphical illustration of the tree structure of this model is given in figure 14. Each patient will follow one path from the root to an end node.

Because of the disadvantages of the reference strategy, it may be prudent to perform a different test-treatment strategy, with a test which is less invasive and has lower costs. In this strategy a non-invasive test will be performed first (e.g. a CTA in our example). The test can be interpretable or uninterpretable. If the test is uninterpretable then the reference test still has to be performed. After the reference test the patient will get the optimal treatment.

If the test is interpretable, then it can give a positive or a negative result. If the test result is positive then we have to decide to treat with treatment *P* (e.g. a stent or CABG in our example), with the risk of harm to patients with a false positive (FP) test result or do the reference test to categorize patients correctly and give them the optimal treatment, but this again involves risks and costs of the reference test.

If the test result is negative then the patient automatically undergoes treatment *N* (e.g. medicines in our example). This time it is not advantageous to consider the reference test again before giving the treatment, because this would negate the advantages of performing the non-invasive test first and would only add extra costs and risks to the procedure. A graphically illustration of the tree structure of this model is given in figure 5.

2.2 Outcome measures

To compare the different test-treatment strategies, we need some quantitative outcome measures as outcomes of our models. These outcomes represents the total benefit and the total costs of the

[1] With a false positive test result, an healthy patient is categorized as having the disease and with a false negative test result, an ill patient is categorized as not having the disease.

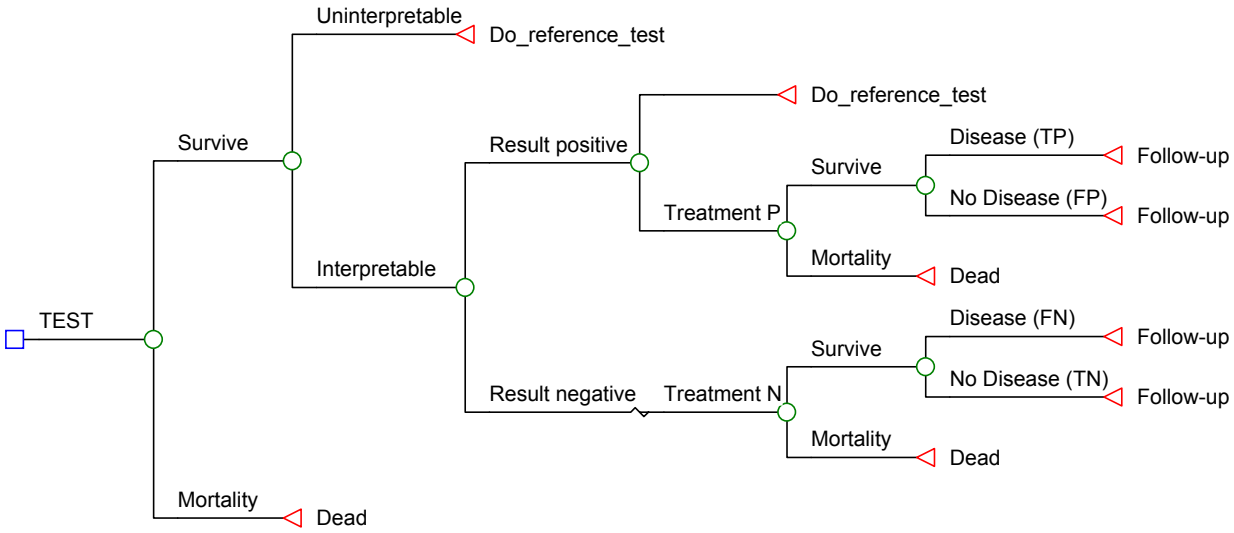

Figure 5: Test strategy

	health care	non-health care	morbidity
test	#	#	#
treatment	#	#	#

Table 1: Short-term costs

procedure. The total benefit will be in quality-adjusted life years (QALYs) [2] and the total costs will be in euros.

The outcome measures consists of two parts; the short-term and the long-term outcomes. The short-term outcome measures are derived from the tests and treatment and the long-term outcome measures are derived from the follow-up. First we will discuss the short-term outcomes.

Short-term costs are divided in health care, non-health care and morbidity costs. The health care costs represent the costs related to providing care within the health care system and include for example hospital admission, diagnostic tests, procedures, outpatient care, and medication. The non-health care costs are the costs unrelated to the health care system and include for example travel costs, time costs, and production losses. Morbidity costs are unexpected costs which are made when the patient for example has a complication as a result of the test or the treatment. See table 1 for an overview.

The benefit in the short-term is in case of mortality of a test or treatment zero. In case of morbidity a one-time disutility, expressed in units of QALYs, is subtracted from the overall QALY

[2] A measure of health outcome which assigns to each period of time a weight, usually ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to dead; these are then aggregated across time periods.
- *Gold M.R., Siegel J.E., Russel L.B., Weinstein M. (eds). Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996.*

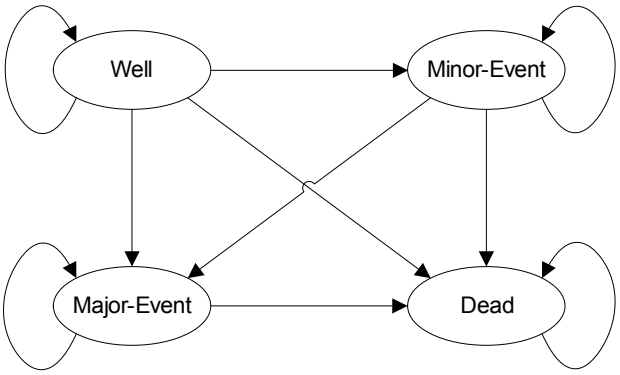

Figure 6: Follow up state-transition diagram

estimate.

To compute the outcome measures for the long-term we will first model the follow up period. We will model this as a Markov process. A patient can be in one of several health states and then can pass from one state to another during each time period, according to probabilities (transition probabilities). In our model we distinguish four different health states in the follow up. The well, minor-event, major-event and the dead state. At the beginning of the follow-up period, a patient starts in one of these health states. From the well state the patient can remain well, but can also have a minor-event, major-event or die. From the minor-event state the patient remains in the minor-event state or can have a major-event or die. In the major-event state a patient cannot recover anymore and will stay in the major-event state or die. Once in the dead state, the patient remains in the dead state. In figure 6 a state-transition diagram is shown.

We merge this state-transition diagram with the decision trees (figures 14 and 5) by adding a recurrent tree to the end nodes of the decision trees. This recurrent tree is given in figure 7 and processes the same properties as the state-transition diagram.

The dead state is an absorbing state, so there the tree ends immediately. At the other states we distinguish first two possibilities; to die or survive from other causes than the disease (e.g. age related, traffic accident, etc...). In case of death an individual goes to the dead state. In the well and minor-event state an event can occur or not. If no event occurs a patient remains in the well state or minor-event state respectively. Otherwise a minor or a major event occur. These events may cause immediate death or not. In case of death the patient goes to the dead state, otherwise (s)he goes respectively to the minor-event or major-event state. In the major-event state, the patient cannot recover anymore and will have an extra probability to die from the major event.

With this tree, we can now calculate the benefits of the follow-up (which are the long-term benefits). To do this calculation patients start their follow up in one of the health states and pass through some cycles (or periods) of the tree until the patient ends in the dead state. For each cycle in the tree the patient gets an added benefit and cost depending on the state of the patient. The added benefit is the utility of a patient multiplied by the period length, which is in QALYs. The utility in the well state, generally one, is higher than the utility of the minor-event state, which is higher than that of the major-event state. In the dead state the utility is zero.

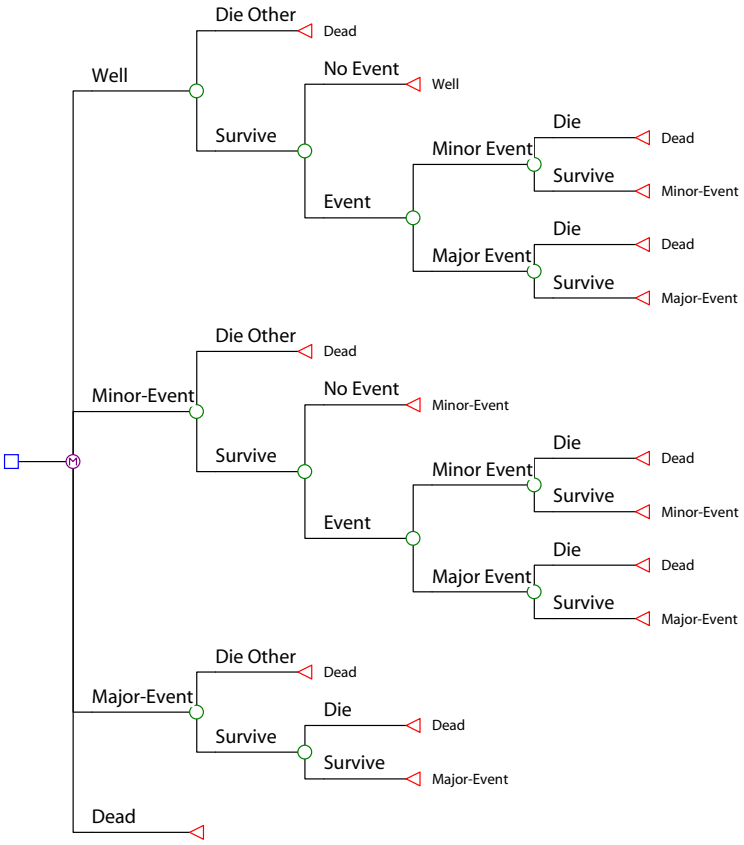

Figure 7: Follow up cycling tree

The added costs for each cycle in the tree are the costs for physician visits, diagnostic consults, etc.... The magnitude of these costs depends on the health state of the patient. In the dead state the added costs are zero.

2.3 Model parameters

After developing the model structure, parameter values need to be determined. At each chance node (the circles) in the tree, there is a probability to go to the upper branch or go to the lower branch. So for example for the reference test strategy (figure 14), we need for the first node the probability of mortality associated with the reference test. We refer to this parameter as $pMortRefTest$. The probability of surviving the reference test is then equal to $1 - pMortRefTest$, because the probabilities must sum to one. For all the branches we need the same type of probability parameters.

In our model we want to calculate all the costs and benefits of a patient during the monitored time. Therefore we need to keep track of the total costs and total benefits. These values are gained by adding (or subtracting) values at each of the nodes of the tree to the total amount of costs/benefits. In our model we introduce the variables $Total\_cost$ and $Total\_benefit$, which

starts at zero and sums all the costs and benefits, respectively, during the whole process. These variables will provide us with the information we need.

At each node where a test or treatment is performed, like the reference test node in figure 14, a value must be added to the total costs. These costs are divided in health care and non-health care costs as mentioned before. We can call these parameters in our example *cHC_RefTest* and *cNHC_RefTest*. The addition of these values is done in the following way:

$$Total\_cost = Total\_cost + cHC\_RefTest + cNHC\_RefTest$$

After the test or treatment, there is a chance of morbidity which can add costs and subtract disutility to the two totals. We call this chance in our example *pMorbRefTest*. Because we are mostly interested in averages, we multiply the morbidity costs (*cMorbRefTest*) with this chance to obtain the average costs per patient. We do this at the survive node in our decision tree in the following way:

$$Total\_cost = Total\_cost + cMorbRefTest * pMorbRefTest$$

Because the morbidity also affects the total benefit of the patient and therefore the total amount of benefit will have to be adjusted too. We introduce *disutilMorbRefTest* as the disutility caused by the morbidity of the reference test and can calculate the new amount of total benefit with the following formula:

$$Total\_benefit = Total\_benefit - disutilMorbRefTest * pMorbRefTest$$

Finally there are benefits and costs accrued during the follow-up period. Each cycle in the Markov subtree gives an added benefit and cost, depending on which health state the patient is in (as mentioned earlier). This is done until all patients are in the death state, or the number of cycles has passed a given amount (*years_FU*). Because years further away in the future are less important than the early years, these added benefit and costs will be discounted (*discount_rate*) to net present value.

A complete list of all used parameters is given in appendix A and the complete model, including all parameters, is given in appendix G.

2.4 Simplified example

In this subsection we will show, after deriving a model, how to calculate the outcome measures. We do this by a simplified example of the reference test strategy, given in the upper tree of figure 8.

The probability, cost and benefit parameters are defined just before the first root. Ad each node costs or disutilities will be added/subtracted when needed.

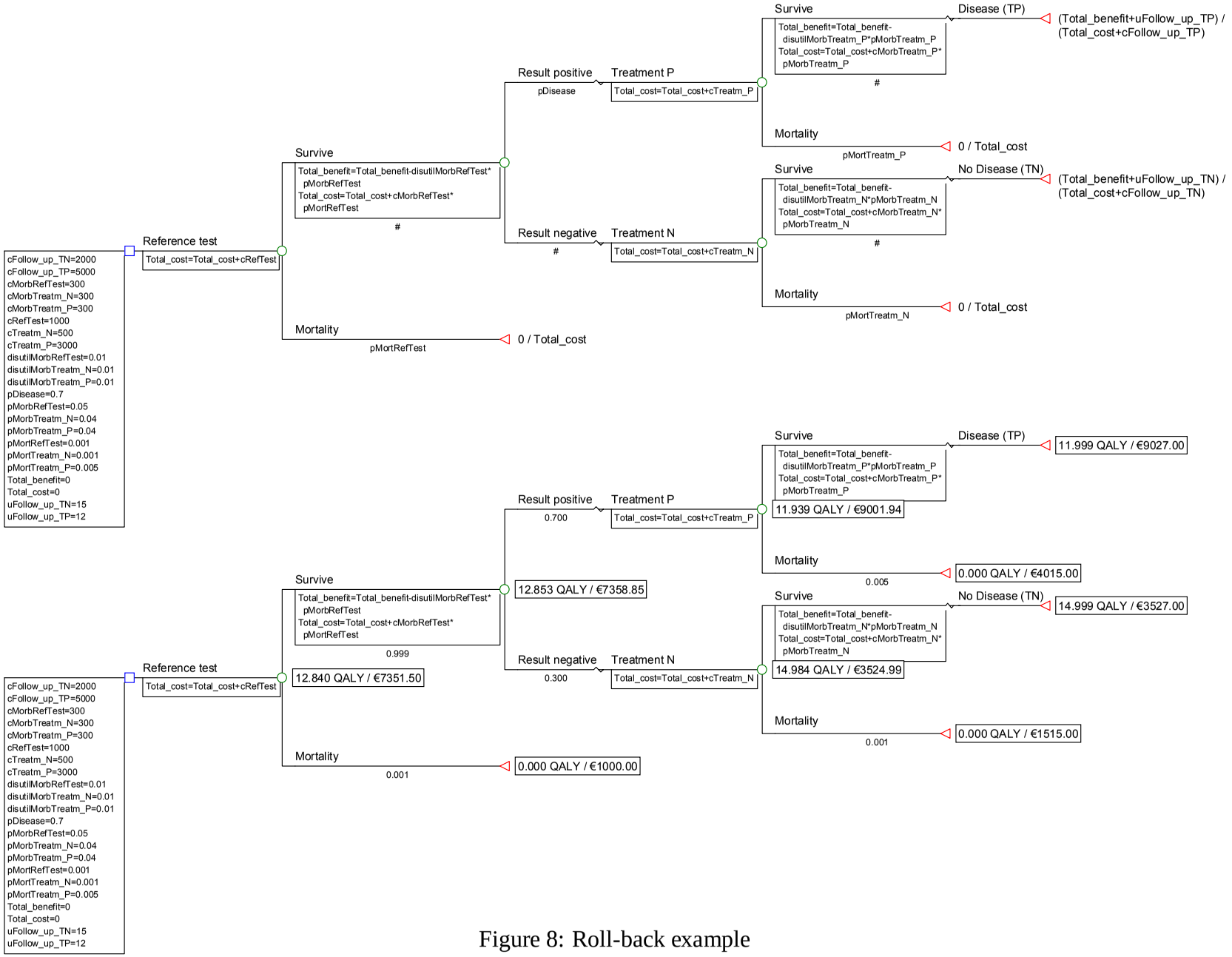

Figure 8: Roll-back example

We don't use a Markov tree for the follow up, but add just a fixed cost and benefit to the $Total\_cost$ and $Total\_benefit$ variables, for illustrative reasons.

First, for all end nodes the expected benefit and expected costs will be calculated. Look at the first end node (Disease (TP)) in the lower tree of figure 8, for the expected benefit and costs you can follow the root node till this end node, and add or subtract all benefits and costs. So the benefit will be:

$$\begin{aligned} & -disutilMorbRefTest * pMorbRefTest \\ & -disutilMorbTreatm\_P * pMorbTreatm\_P + uFollow\_up\_TP \\ = \; & -0.01 * 0.05 - 0.01 * 0.04 + 12 \\ = \; & 11.999 \; QALY \end{aligned}$$

and the costs will be:

$$\begin{aligned} & cRefTest + cMorbRefTest * pMorbRefTest + cTreatm\_P \\ & +cMorbTreatm\_P * pMorbTreatm\_P + cFollow\_up\_TP \\ = \; & 1000 + 300 * 0.05 + 3000 + 300 * 0.04 + 5000 \\ = \; & €9027.00 \end{aligned}$$

For all other end nodes there will be similar formulas, only after immediate death of the test or treatment, the total benefit is set to zero. The other expected values can be calculated beginning at the end nodes and folding back until the root node is reached. If we consider the "Treatment P" node for example, the probability of survival is 0.995 and the probability of mortality is 0.005. Therefore the expected benefit and costs are 0.995 times the expected benefit and costs of the end node "Disease (TP)" plus 0.005 times the expected benefit and costs of the end node "Mortality" (the top one). This gives an expected benefit of $0.995 * 11.999 + 0.005 * 0 = 111.939$ *QALY* and an expected cost of $0.995 * 9027.00 + 0.005 * 4015.00 =$€9001.94.

All other nodes can be calculated with this method until the expected benefit and costs of the root node is known. In this case the expected benefit and costs for a patient who will undergo the reference test strategy is resp. 12.840 QALY and €7351.50.

The same can be done for the test strategies. After defining a willingness to pay (WTP), the best strategy can be indicated. The WTP is the quantity of money you are willing to pay for one QALY. By this WTP we can transform the expected benefit from QALYs to euros. For each strategy the net monetary benefit (NMB) can then be calculated. NMB (euros) = expected benefit (QALYs) * WTP (euro/QALY) - expected costs (euros). Because of this transformation, it is possible to compare the different strategies on a one-to-one scale.

In this simplified example we added fixed benefits and costs instead of using a Markov tree as follow up. With the Markov tree the expected benefit and costs can be calculated (and in our whole model, we use these expected values instead of the fixed values as in the simplified example).

In our calculation we use the four different health states of our follow-up model. Initially, a patient starts there follow-up in one of these states and passes trough states several times until the patient arrives in the dead state. We can also calculate expected values, to do this we divide the patients in proportions over the different states. One cycle later these proportions change, depending on the transition probabilities, and so on. For each cycle we add discounted expected benefit and discounted expected costs till the proportion in the dead state is one or the total number of cycles exceeds the follow up period (e.g. 5 years). These added discounted benefit and costs are calculated as follows:

$$benefit = pWell * \frac{uWell}{(1+r)^t} + pMinor * \frac{uMinor}{(1+r)^t} + pMajor * \frac{uMajor}{(1+r)^t}$$

$$cost = pWell * \frac{cWell}{(1+r)^t} + pMinor * \frac{cMinor}{(1+r)^t} + pMajor * \frac{cMajor}{(1+r)^t}$$

With $pWell =$ proportion in well state, $pMinor =$ proportion in minor event state, $pMajor =$ proportion in major event state, $uWell =$ utility in well state, $uMinor =$ utility in minor event state, $uMajor =$ utility in major event state, $cWell =$ costs in well state, $cMinor =$ costs in minor event state, $cMajor =$ costs in major event state, $r =$ discount rate and $t =$ cycle number. Sum these benefit and costs over all cycles and we derive the expected benefit and cost for the follow-up.

2.5 Parameter distributions

In the simplified example all parameters were represented by fixed numbers. But in real life these parameters should be estimated by data collected from literature or from a study. In the simplified example the probability of mortality of the reference test is 0.001. This number could for example be derived by study data of 1000 patients in which one of these 1000 patients did not survive the reference test. But this one patient out of thousand patients could be just coincidence; in another trial this number could be zero, two, three or whatever. So this probability of 0.001 is not certain, it could be less or it could be more.

Therefore each parameter should not be represented by a fixed number, but by an underlying distribution. This raises the question on which distribution to use for which parameters. We use proposed distributions by Briggs et al. [2]. However other kinds of distributions are possible.

2.5.1 Probability parameters

Probabilities are mostly based on the observed proportion of the event of interest (e.g., *a* successes out a trial of *n*). Therefore you should think of a binomial distribution. However, because

this is a discrete distribution and we have a continuous parameter environment, we use a Beta distribution:

$$\begin{aligned} X &\sim Beta(\alpha,\beta) \\ \mu &= \frac{\alpha}{\alpha+\beta} \\ \sigma &= \sqrt{\frac{\alpha\beta}{(\alpha+\beta+1)(\alpha+\beta)^2}}, \end{aligned}$$

with μ the mean and σ the standard deviation.

The probability of mortality of the reference test in our simplified example therefore gets a $Beta(\alpha = 1, \beta = 999)$ distribution (with α the number of deaths and β the number of survivors).

If literature is used for estimating the parameter, often only a mean value and a standard deviation (or confidence interval) is given. The parameters α and β can then be approximated from the mean and standard deviation:

$$\begin{aligned} \alpha &= \frac{\mu^2 * (1-\mu)}{\sigma^2} \\ \beta &= \frac{\mu * (1-\mu)}{\sigma^2} - \alpha \end{aligned}$$

2.5.2 Cost parameters

For the cost parameters a log-normal distribution is chosen:

$$\begin{aligned} X &\sim LogNormal(\mu,\sigma) \\ \mu &= \ln(median) \\ \sigma &= \sqrt{\ln\left(\frac{mean}{median}\right) * 2}, \end{aligned}$$

with μ the mean of logs and σ the standard deviation of logs. The parameters μ and σ can be approximated as above if the mean and median ($<$ mean) is known.

The main reason that the log-normal distribution is chosen, is that the log-normal distribution as well as the costs can not get negative values. But also a normal (with or without bounds), an uniform or a triangle distribution are commonly used.

2.5.3 Benefit parameters

The benefits are less tangible. It is very hard to value the utilities (the health-related quality of life) for each health state. If the patient is well, then the utility is usually one. But the utility of

a patient with e.g. a stroke is less self-evident. Utilities can be obtained using preference-based methods, among patients or society, such as the standard gamble rating scale or time-trade-off. Sometimes expert opinions are used if the utilities of specific health states have not been reported in the literature. Because the utilities are less tangible, a simple distribution is chosen for the benefit parameters; a triangle distribution (with the parameters minimum, likeliest and maximum).

2.5.4 Relative risk parameters

Some parameters in the model are hard to define and are not documented. Also a lot of these parameter are dependent of other parameters. In our model, parameters of patients with a true positive test result depend on patients with a false negative test result. They both have the disease, but patients with a false negative test result may be harmed because they do not receive their optimal treatment. Therefore we assume that the probability of occurring and dieing from a minor or major event is equal or larger for a patient with a false negative test result than for a patient with a true positive test result. Also we assume that the utility in the well state is equal or lower for a patient with a false negative test result compared with a patient with a true positive test result.

To model these properties we introduce relative risk parameters. All probabilities and utilities for a patient with a false negative test result are equal to the probabilities and utilities of a patient with a true positive test result multiplied by a relative risk (≥ 1 for the probabilities and ≤ 1 for the utility in the well state). The same yields for a patient with a true negative test result versus a patient with a false positive test result and the utility for the major-event state versus the minor-event state. All relative risk parameters are also given in appendix A.

For the relative risk parameters a normal distribution (with parameters μ and σ) is chosen.

2.5.5 Life-table

In the follow-up cycling tree (figure 7), a probability parameter *pDieOther* is used. This is the probability per year to die of other causes then the disease. This probability will be higher as the patient become older. Therefore an age dependent life-table will be used, which shows a population (male, female, European, etc...) mortality rate as a function of age. This table is collected from a statistical organization (e.g. Centraal Bureau voor de Statistiek (CBS) in the Netherlands). The probability parameter *pDieOther* changs over time depending on the cycle stage and starting age as defined in the life-table.

3 Value of information analysis

After defining our model, we can perform the value of information analysis. Currently, uncertainty surrounds all model parameters (they are not exactly known and have an underlying distribution). By obtaining more information about the real parameter values (by doing more research), the uncertainty of these parameter values can be reduced. By lowering the uncertainty of these parameters, we will improve the accuracy of our model, which will lead to better strategic decisions.

The value of information is the incremental benefit of the optimal strategy with additional information versus the optimal strategy without additional information. Is the optimal strategy the same after obtaining more information, then the additional information was useless (the VOI is then equal to zero). But if the optimal strategies differs, then the additional information was useful (so with the additional information we could make a better decision). The VOI is then the difference in net monetary benefit (NMB) or net health benefit between these optimal strategies. We will express the VOI as the NMB.

Before obtaining additional information, it is not known what the VOI shall be. But the expected value of information can be estimated, for different kinds of information, as shown in the following sections.

3.1 Expected value of perfect information

First we will discuss the expected value of perfect information (EVPI). With perfect information we mean that all parameter values will be exactly known. The EVPI is the difference between the expected net monetary benefit (NMB) of optimal strategy with perfect information and the expected NMB of optimal strategy without perfect information. Without perfect information over the real parameter values, the decision maker should choose the strategy with the greatest expected NMB.

We use the same notations as in Groot Koerkamp at al. [3]. Define θ as the vector with all model parameters and $a \in \{\text{reference test,test A},\ldots\}$ as all different strategies. $B(a,\theta)$ is the net monetary benefit of strategy a if the parameters take the value θ.[3] Because the 'real' θ is unknown we should integrate over the joint distribution of θ to derive the expected NMB of strategy a; $\mathbb{E}_\theta B(a,\theta)$. We maximize over all strategies to derive the expected NMB of optimal strategy with current information:

$$\max_a \mathbb{E}_\theta B(a,\theta).$$

If θ was the vector with the 'real' parameter values, then the NMB of the optimal strategy is

[3] $B(a,\theta)$ will be calculated as in the simplified example (section 2.4).

$\max_a B(a,\theta)$. But because the 'real' parameter values are unknown we should average this expression over the joint distribution of θ and we get

$$\mathbb{E}_\theta \max_a B(a,\theta)$$

as the expected NMB of the optimal strategy with perfect information.

The EVPI is the difference between these two expressions:

$$EVPI = \mathbb{E}_\theta \max_a B(a,\theta) - \max_a \mathbb{E}_\theta B(a,\theta). \tag{1}$$

Because $B(a,\theta)$ is a very complex function, it is not possible (so far) to calculate equation 1 analytically. Therefore we use Monte Carlo simulation. First we will rewrite equation 1 in terms of opportunity loss. Opportunity loss is the difference between the NMB of the strategy that is optimal given the 'real' parameter values θ and the NMB of the strategy a^* that was optimal at baseline.

$$\begin{aligned} EVPI &= \mathbb{E}_\theta \max_a B(a,\theta) - \max_a \mathbb{E}_\theta B(a,\theta) \\ &= \mathbb{E}_\theta \max_a B(a,\theta) - \mathbb{E}_\theta B(a^*,\theta) \\ &= \mathbb{E}_\theta [\max_a B(a,\theta) - B(a^*,\theta)] \\ &= \mathbb{E}_\theta [\text{opportunity loss}] \end{aligned}$$

With Monte Carlo simulation we can estimate the expected opportunity loss. For each randomly drawn of θ we can imagine it is the 'real' parameter values. The opportunity loss of the drawn value is the difference between the NMB of the optimal strategy given this value of θ and the NMB of strategy a^* that was optimal at baseline. The expected opportunity loss (and so the EVPI) is estimated as the average over many random draws. The algorithm is given in appendix B.

If the EVPI is low, then we expect that only a very low benefit will be gained with further research (obtaining more information).[4] So we will then choose the strategy with the greatest expected net monetary benefit. But if the EVPI is high we should consider whether to perform more research.

3.2 Expected value of partial perfect information

Next we should consider which parameters gives the most information. This can be done by calculating the expected value of partial perfect information (EVPPI). Suppose we have now perfect information of a subset of all parameters: $\theta_I \supset \theta$. And θ_C is the complement of θ_I. Now with perfect information of this subset θ_I the expected NMB of the optimum decision is given

[4] When to categorize the EVPI as to low will depending on the prevalence of disease and the population to benefit. How bigger the population, how bigger the benefit to be gained.

by $\max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta)$. But because the real parameters for θ_I are unknown we should average this expression over the joint distribution of θ_I and we get $\mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta)$ as the expected NMB of the optimal strategy with partial perfect information. So we derive the following formula for the EVPPI:

$$EVPPI(\theta_I) = \mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta) - \max_a \mathbb{E}_{\theta} B(a,\theta) \tag{2}$$

We first rewrite equation 2 in terms of opportunity loss, to be able to do a two-level Monte Carlo simulation for estimating the EVPPI.

$$\begin{aligned}
EVPPI(\theta_I) &= \mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta) - \max_a \mathbb{E}_{\theta} B(a,\theta) \\
&= \mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta) - \mathbb{E}_{\theta} B(a^*,\theta) \\
&= \mathbb{E}_{\theta_I} [\max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta) - \mathbb{E}_{\theta_C|\theta_I} B(a^*,\theta)] \\
&= \mathbb{E}_{\theta_I} [\max_a \mathbb{E}_{\theta_C|\theta_I} [B(a,\theta) - B(a^*,\theta)]] \\
&= \mathbb{E}_{\theta_I} [\text{opportunity loss of not knowing } \theta_I]
\end{aligned}$$

For each randomly drawn of θ_I we can imagine it is the 'real' parameter value. For each θ_I we will draw multiple times a θ_C to calculate the expected NMB of all strategies. The opportunity loss of not knowing the drawn θ_I is the difference of the expected NMB of optimal strategy and the expected NMB of the baseline strategy a^*. By averaging the opportunity loss over many random draws of θ_I's, we estimate the expected opportunity loss (and so the EVPPI). The algorithm is given in appendix C.

By varying θ_I and calculating the EVPPIs we obtain information about which parameter (set) provides the highest value when more research is performed.

3.3 Expected value of partial sampling information

It is impossible to eliminate all parameter uncertainty (of the subset θ_I), because this will require a study with infinite sample size. The EVPI and EVPPIs therefore give an upper bound of the expected benefit of doing further research. The larger the sample size, the closer the expected benefit will reach the upper bounds. In fact, the larger the sample size, the larger the reduction of the kurtosis (degree of peakedness) of the underlying parameter distributions (so reducing uncertainty).

After defining the most valuable parameters, new data (D) could be obtained for this set of parameters by doing more research. With this new data we can update the underlying parameter distributions.

If the data are known in advance the expected NMB of the optimal strategy will be given by $\max_a \mathbb{E}_{\theta_C,(\theta_I|D)} B(a,\theta)$. However, because the data are not known, we should average this expression over the joint distribution of obtaining data and we get $\mathbb{E}_D \max_a \mathbb{E}_{\theta_C,(\theta_I|D)} B(a,\theta)$ as the

expected NMB of the optimal strategy with partial sampling information (EVPSI). So we derive the following formula for the EVPSI:

$$EVPSI(\theta_I, n) = \mathbb{E}_D \max_a \mathbb{E}_{\theta_{C,(\theta_I|D)}} B(a,\theta) - \max_a \mathbb{E}_\theta B(a,\theta), \tag{3}$$

with n the sample size.

Again we can rewrite this equation first in terms of opportunity loss:

$$\begin{aligned} EVPSI(\theta_I, n) &= \mathbb{E}_D \max_a \mathbb{E}_{\theta_{C,(\theta_I|D)}} B(a,\theta) - \max_a \mathbb{E}_\theta B(a,\theta) \\ &= \mathbb{E}_D \max_a \mathbb{E}_{\theta_{C,(\theta_I|D)}} B(a,\theta) - \mathbb{E}_\theta B(a^*,\theta) \\ &= \mathbb{E}_D [\max_a \mathbb{E}_{\theta_C,\theta_I|D} B(a,\theta) - \mathbb{E}_{\theta_C,\theta_I|D} B(a^*,\theta)] \\ &= \mathbb{E}_D [\max_a \mathbb{E}_{\theta_C,\theta_I|D} [B(a,\theta) - B(a^*,\theta)]] \\ &= \mathbb{E}_D [\text{opportunity loss of not knowing the new data } D] \end{aligned}$$

It is difficult to estimate this equation 3, because the joint distribution of the new data D is unknown. We will show how to derive the EVPSI in the case of just one Beta distributed model parameter of interest.

To generate a random D, first the θ_I should be drawn from its distribution (and imagine it is the 'real' parameter value). The new drawn D then has a Beta distribution, with parameters $\alpha_D = n \cdot \theta_I$ and $\beta_D = n(1-\theta_I)$. With these data D we can update the distribution of $\theta_I|D$ by simply adding up the α's and β's. So $\alpha_{new} = \alpha_{old} + \alpha_D$ and $\beta_{new} = \beta_{old} + \beta_D$.

For each D we will draw multiple times a θ_C and a θ_I (from the distribution of $\theta_I|D$) to calculate the expected NMB of all strategies. The opportunity loss of not knowing the new data D is the difference of the expected NMB of optimal strategy and the expected NMB of the baseline strategy a^*. By averaging the opportunity loss over many random draws of D, we estimate the expected opportunity loss (and so the EVPSI). The algorithm is given in appendix D and can also be used for sets of parameters.

In the case of another (then the Beta) distributed parameter of interest, the new drawn D will also have another distribution. And updating the distribution $\theta_I|D$ will be different. We refer to the paper of Ades et al. [1] for the methods.

3.4 Comments

For the ART-group, the software package 'Treeage Pro' is generally used for model building and cost-effectiveness studies. Treeage Pro contains also Monte Carlo simulations with which we are able to estimate the EVPI and EVPPI. It is not possible to derive the EVPSI with this software yet. Therefore we will focus on the EVPI and EVPPI only.

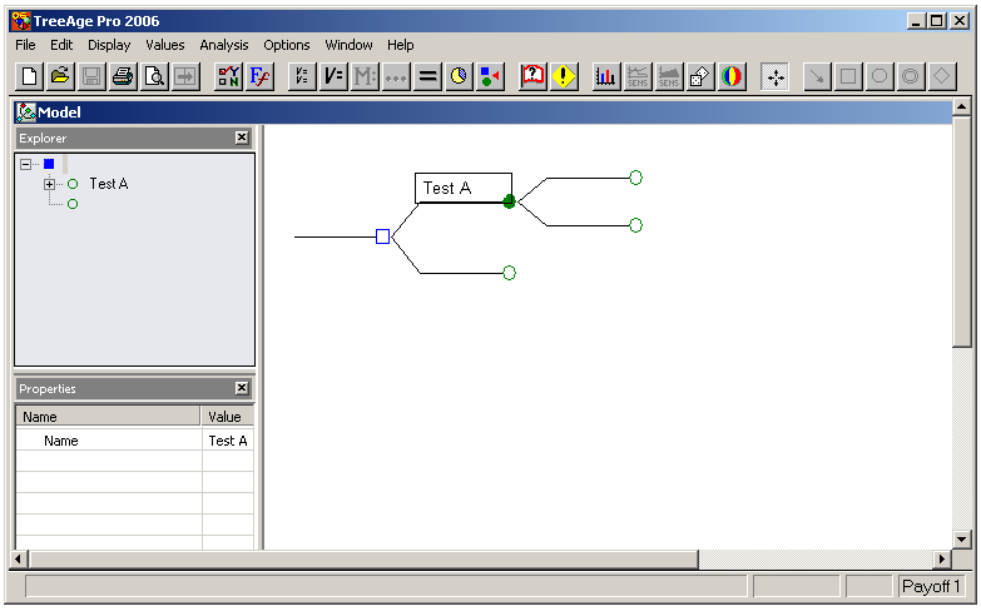

Figure 9: Screen shot of Treeage pro

4 Implementation

For the implementation of the model and value of information analysis the software package ‘Treeage Pro’ was used. Treeage Pro is specifically developed for making and evaluating decision trees. A screen shot of Treeage Pro has been given in figure 9. Using this software the model (as shown in section 2) is able to be created and the EVPI and EVPPI can be estimated by Monte Carlo simulations.

The disadvantages of using Treeage pro are the changes in variables and distributions and the adjustment of which parameters to include in the EVPPI analysis, which is very time consuming and user unfriendly. The user has to do multiple actions over again for each change or adjustment. Because of this disadvantage we made a user friendly Microsoft Excel sheet. In Excel, visual basic macro’s can be used to communicate with Treeage Pro. With these macro’s the user does not have to do multiple actions over again but can change or adjust everything at once.

The Excel sheet we made, consists of three parts: A view tree; a modify tree and an analyze tree. By clicking on the ‘View Tree’ button, the model will be shown (figure 10 for a screen shot).

By clicking on the ‘Modify Tree’ button, the modify sheet will be shown (figure 11 for a screen shot). All the inputs that can be changed are in white boxes. At the top of the sheet, the user can give names to the reference test, the other test, treatment P, treatment N, minor event and major event. At the bottom of the sheet a table with all the parameters is given; divided into multiple columns. In the column labeled ‘Parameter name’ the parameter name is given. In the column labeled ‘Description’ the description of that parameter is given, with the names the user gave to the reference test, other test, etc.... If a parameter is of interest for the EVPPI calculation it can

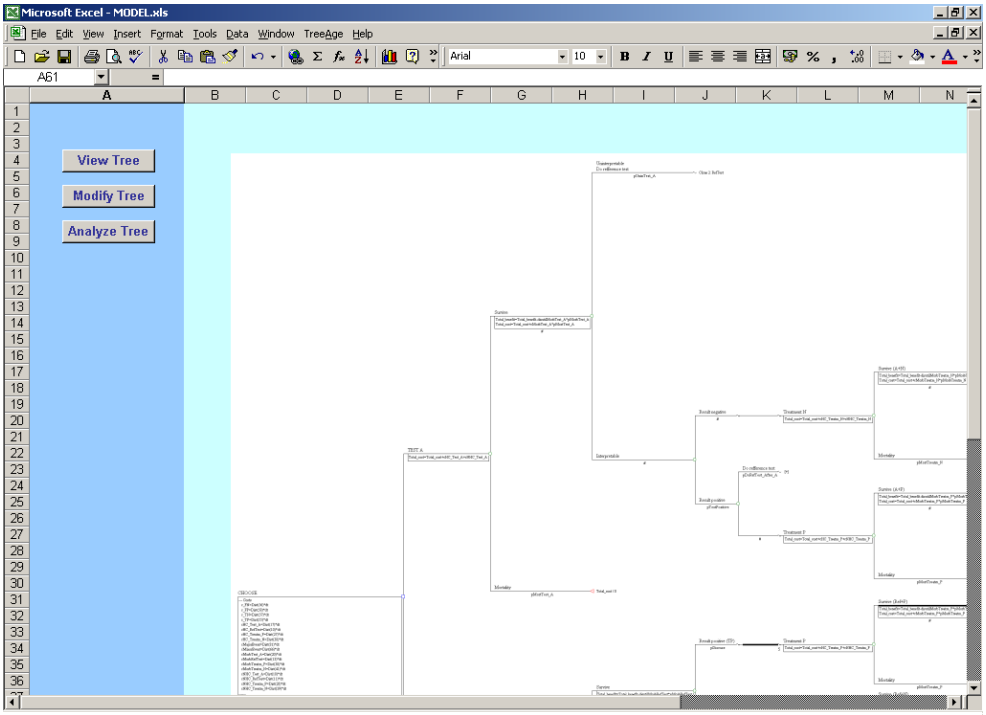

Figure 10: Screen shot of Excel ‘View Tree’ sheet

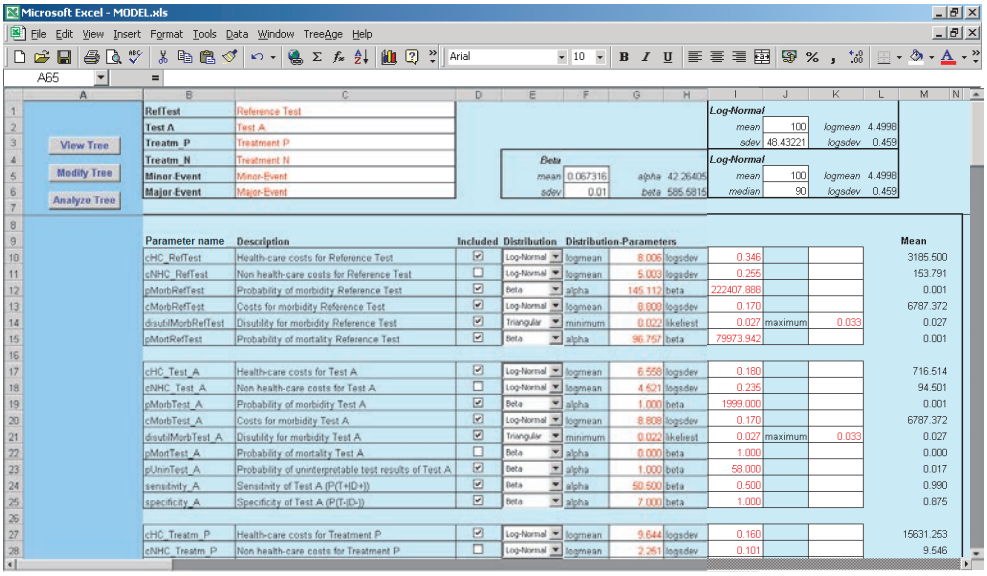

Figure 11: Screen shot of Excel ‘Modify Tree’ sheet

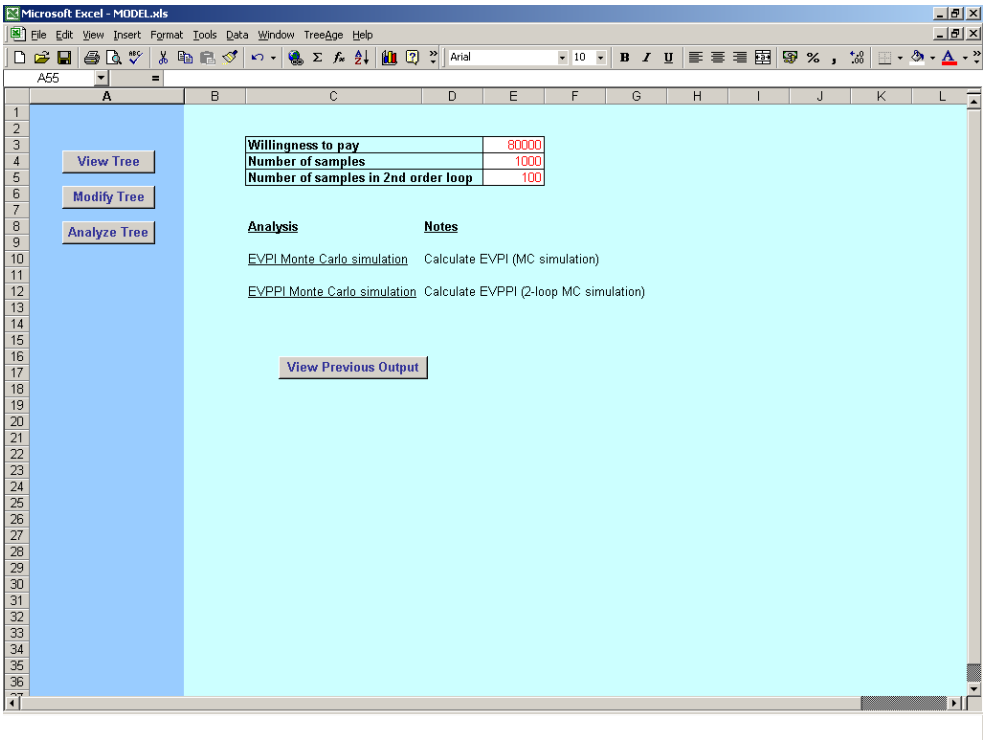

Figure 12: Screen shot of Excel ‘Analyze Tree’ sheet

be included by clicking the check box in the column labeled ‘Included’. In the column labeled ‘Distribution’ the user can choose between different distributions (the beta, log-normal, normal, triangular or uniform distribution) or simply choose a fixed number by selecting from the combo box. In the column labeled ‘Distribution-parameters’ the right distribution-parameters or a fixed number can be filled in. If only the mean and standard deviation for the beta distribution or only the mean and standard deviation/median for the log-normal distribution is available, then the user can convert these numbers to the right distribution-parameters at the top of the sheet. Finally, in the column labeled ‘Mean’, the mean value of that parameter will be shown. If all parameters are changed correctly, the user should click on the ‘Submit’ button (at the bottom of the sheet) to submit all changes to Treeage Pro at once.

By clicking on the ‘Analyze Tree’ button, the analyze sheet will be shown (figure 12 for a screen shot). In this sheet the willingness to pay, number of samples[5], and number of samples in 2^{nd} order loop[6] can be set determined by the user.

The EVPI and the EVPPI calculations can be performed by clicking on ‘EVPI Monte Carlo Simulation’ and ‘EVPPI Monte Carlo Simulation’, respectively. The user will be shown the output automatically. The output consist of an histogram at the top of the sheet and some statistics at the bottom. The histogram shows the expected NMB of the strategy which was optimal at baseline versus the EVPI or EVPPI (also in NMB). The statistics contains the mean, standard

[5]number of samples $= N$ in the algorithms for EVPI and EVPPI calculation (Appendix B and C)
[6]number of samples in 2^{nd} order loop $= M$ in the algorithm for EVPPI calculation (Appendix C)

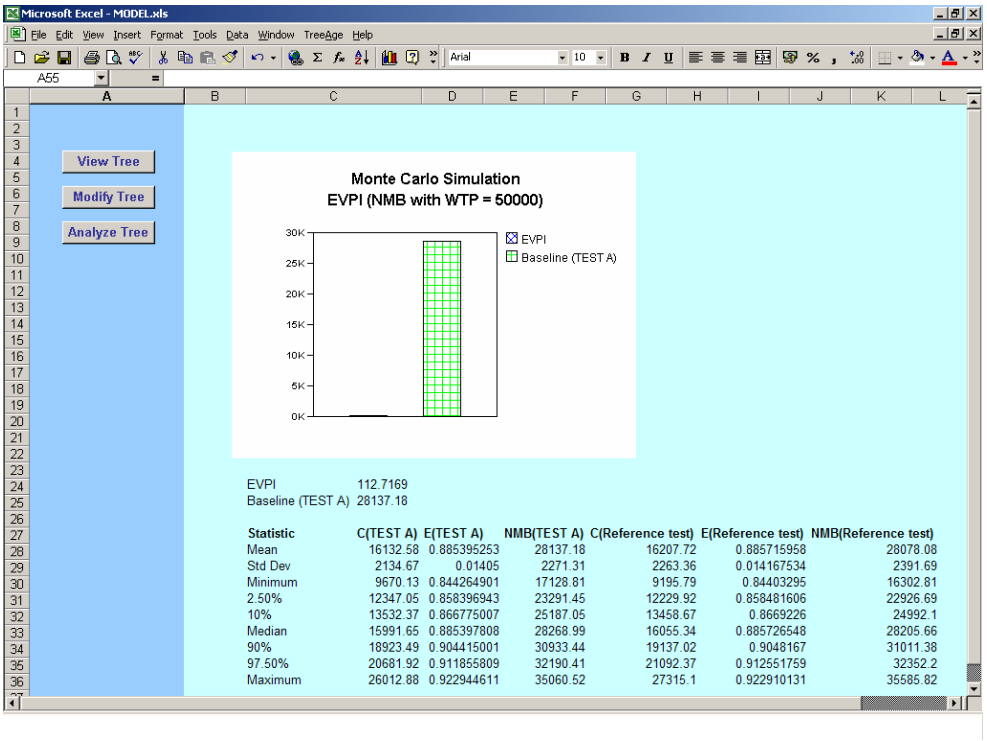

Figure 13: Screen shot of Excel ‘Output’ sheet

deviation and the quantiles of the costs, benefits and NMB of all strategies (See figure 13 for a screen shot of the outputs).

4.1 Example Coronary Artery Disease

We now continue our example of patients with suspected coronary artery disease (in section 2.1). There were two diagnostic tests available, coronary angiography and computed tomographic angiography (CTA). The data for most parameter distributions was collected from other members of the ART research group. The missing parameters were estimated. Because all parameter distributions should be based on evidence, this example is only for illustrative reasons. All used input data can be found in appendix E.

An EVPI estimation with a Monte Carlo simulation with $10,000$ samples was performed. We used a willingness to pay of $50,000$ euro. The optimal strategy at baseline is to perform the CTA test, which has an expected NMB of $28,137$ euro. The reference strategy, coronary angiography, has an expected NMB of $28,078$ euro. The statistics of the two test strategies are given in table 2.

The EVPI is 113 euro, which means that if all parameter uncertainty is eliminated, we expect an increase of 113 euro in the total NMB. This 113 euro increase is per individual patient. The next step is to apply this increase in NMB to the total population to benefit. The population size depends on the countries in which the the new study is applicable and on the number of

Statistic	Costs(CTA)	Benefit(CTA)	NMB(CTA)
Mean	16132.58	0.885395253	28137.18
Std Dev	2134.67	0.01405	2271.31
Minimum	9670.13	0.844264901	17128.81
2.50%	12347.05	0.858396943	23291.45
10%	13532.37	0.866775007	25187.05
Median	15991.65	0.885397808	28268.99
90%	18923.49	0.904415001	30933.44
97.50%	20681.92	0.911855809	32190.41
Maximum	26012.88	0.922944611	35060.52

Statistic	Costs(CABG)	Benefits(CABG)	NMB(CABG)
Mean	16207.72	0.885715958	28078.08
Std Dev	2263.36	0.014167534	2391.69
Minimum	9195.79	0.84403295	16302.81
2.50%	12229.92	0.858481606	22926.69
10%	13458.67	0.8669226	24992.10
Median	16055.34	0.885726548	28205.66
90%	19137.02	0.9048167	31011.38
97.50%	21092.37	0.912551759	32352.20
Maximum	27315.1	0.922910131	35585.82

Table 2: CAD model outputs

years the study is of relevance. Because of the rapid advances in technology we expect a newer and better technique to be found. Define Q_y as the number of patients to benefit in year y, with $y = 1,2,\ldots,H$ (H the effective lifetime for the technology (CTA, CABG)) the population EVPI is then:

$$\text{Population } EVPI = EVPI * \sum_{y=1}^{H} \frac{Q_y}{(1+r)^y}$$

with r the discount rate.

If one supposes the total population size is $10,000$ patients and a relevance of only one year, then the Population EVPI is $130 \cdot 10,000 = 1,300,000$. This Population EVPI is an upper bound of the expected benefit of doing more research. If a new study has a cost of more than $1,300,000$ euro, then the study is not justified. If the study costs are lower, the EVPPI should be calculated for the group of parameters the study is applicable, to check if the new study is justified.

4.2 Conclusions

We are able to do EVPI and EVPPI calculations to determine whether a new diagnostic study provides sufficient information to justify research funding. However the EVPI and EVPPI gives only an upper bound of the expected benefit of the new study. Therefore the next step is to calculate the expected value of partial sampling information (EVPSI(n)). This is the expected

benefit of doing a research study with a sample size of n. The EVPSI is not an upper bound and will give the 'real' expected benefit of the new study. Using EVPI and EVPPI, priorities can be given to guide future diagnostic research should the need arise to chose between multiple diagnostic studies.

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[3] Groot Koerkamp B, Hunink MGM, Stijnen T, Weinstein MC. *Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods*. Health Economics (in press); m.hunink@erasmusmc.nl

[4] Hunink MGM, Glasziou PP. *Decision making in health and medicine: Integrating evidence and values*. Cambridge University Press, 2001.

A Parameter variables

Variable name	Description
cHC_RefTest	Health-care costs for reference test
cNHC_RefTest	Non health-care costs for reference test
pMorbRefTest	Probability of morbidity reference test
cMorbRefTest	Costs for morbidity reference test
disutilMorbRefTest	Disutility for morbidity reference test
pMortRefTest	Probability of mortality reference test
cHC_Test_A	Health-care costs for new test
cNHC_Test_A	Non health-care costs for new test
pMorbTest_A	Probability of morbidity new test
cMorbTest_A	Costs for morbidity new test
disutilMorbTest_A	Disutility for morbidity new test
pMortTest_A	Probability of mortality new test
pUninTest_A	Probability of uninterpretable test results of new test
sensitivity_A	Sensitivity of new test (P(D+—T+))
specificity_A	Specificity of new test (P(D-—T-))
cHC_Treatm_P	Health-care costs for treatment P
cNHC_Treatm_P	Non health-care costs for treatment P
pMorbTreatm_P	Probability of morbidity treatment P
cMorbTreatm_P	Costs for morbidity treatment P
disutilMorbTreatm_P	Disutility for morbidity treatment P
pMortTreatm_P	Probability of mortality treatment P
pTreatmP_Minor_TP	Probability of starting follow up in minor event for a patient with disease and treatment P
pTreatmP_Minor_FP	Probability of starting follow up in minor event for a patient without disease and treatment P
pTreatmP_Major_TP	Probability of starting follow up in major event for a patient with disease and treatment P
pTreatmP_Major_FP	Probability of starting follow up in major event for a patient without disease and treatment P
cHC_Treatm_N	Health-care costs for treatment N
cNHC_Treatm_N	Non health-care costs for treatment N
pMorbTreatm_N	Probability of morbidity treatment N
cMorbTreatm_N	Costs for morbidity treatment N
disutilMorbTreatm_N	Disutility for morbidity treatment N
pMortTreatm_N	Probability of mortality treatment N
pTreatmN_Minor_TN	Probability of starting follow up in minor event for a patient without disease and treatment N
pTreatmN_Minor_FN	Probability of starting follow up in minor event for a patient with disease and treatment N
pTreatmN_Major_TN	Probability of starting follow up in major event for a patient without disease and treatment N
pTreatmN_Major_FN	Probability of starting follow up in major event for a patient with disease and treatment N

Variable name	Description
pDisease	Prior probability of disease
discount_rate	Discount rate per year for costs and utilities for future years
dt	Cycle length in follow up period
years_FU	Total years of modeling follow up
pDoRefTest_After_A	The proportion of doing the reference test after a positive test result of the new test
c_TP	Costs per year in well state for a patient with disease and treatment P
c_FN	Costs per year in well state for a patient with disease and treatment N
c_TN	Costs per year in well state for a patient without disease and treatment N
c_FP	Costs per year in well state for a patient without disease and treatment P
u_TP	Utility per year in well state for a patient with disease and treatment P
u_FN	Utility per year in well state for a patient with disease and treatment N
RR_u_FN	Relative risk u_FN vs. u_TP (≤ 1)
u_TN	Utility per year in well state for a patient without disease and treatment N
u_FP	Utility per year in well state for a patient without disease and treatment P
RR_u_FP	Relative risk u_FP vs. u_TN (≤ 1)
cMinorEvent	Costs per year in minor event state
pMinorEvent_TP	Probability per year of occurring a minor event for a patient with disease and treatment P
pMinorEvent_FN	Probability per year of occurring a minor event for a patient with disease and treatment N
RR_pMinorEvent_FN	Relative risk pMinorEvent_FN vs. pMinorEvent_TP (≥ 1)
pMinorEvent_TN	Probability per year of occurring a minor event for a patient without disease and treatment N
pMinorEvent_FP	Probability per year of occurring a minor event for a patient without disease and treatment P
RR_pMinorEvent_FP	Relative risk pMinorEvent_FP vs. pMinorEvent_TN (≥ 1)
pDieMinorEvent_TP	Probability of dying of occurring a minor event state for a patient with disease and treatment P
pDieMinorEvent_FN	Probability of dying of occurring a minor event state for a patient with disease and treatment N
RR_pDieMinorEvent_FN	Relative risk pDieMinorEvent_FN vs. pDieMinorEvent_TP (≥ 1)
pDieMinorEvent_TN	Probability of dying of occurring a minor event state for a patient without disease and treatment N
pDieMinorEvent_FP	Probability of dying of occurring a minor event state for a patient without disease and treatment P
RR_pDieMinorEvent_FP	Relative risk pDieMinorEvent_FP vs. pDieMinorEvent_TN (≥ 1)
uMinorEvent	Utility per year in the minor event state

Variable name	Description
cMajorEvent	Costs per year in major event state
pMajorEvent_TP	Probability per year of occurring a major event for a patient with disease and treatment P
pMajorEvent_FN	Probability per year of occurring a major event for a patient with disease and treatment N
RR_pMajorEvent_FN	Relative risk pMajorEvent_FN vs. pMajorEvent_TP (≥ 1)
pMajorEvent_TN	Probability per year of occurring a major event for a patient without disease and treatment N
pMajorEvent_FP	Probability per year of occurring a major event for a patient without disease and treatment P
RR_pMajorEvent_FP	Relative risk pMajorEvent_FP vs. pMajorEvent_TN (≥ 1)
pDieMajorEvent_TP	Probability of dying of occurring a major event state for a patient with disease and treatment P
pDieMajorEvent_FN	Probability of dying of occurring a major event state for a patient with disease and treatment N
RR_pDieMajorEvent_FN	Relative risk pDieMajorEvent_FN vs. pDieMajorEvent_TP (≥ 1)
pDieMajorEvent_TN	Probability of dying of occurring a major event state for a patient without disease and treatment N
pDieMajorEvent_FP	Probability of dying of occurring a major event state for a patient without disease and treatment P
RR_pDieMajorEvent_FP	Relative risk pDieMajorEvent_FP vs. pDieMajorEvent_TN (≥ 1)
pDieMajor_TP	Probability per year of dying from the major event state for a patient with disease and treatment P
pDieMajor_FN	Probability per year of dying from the major event state for a patient with disease and treatment N
RR_pDieMajor_FN	Relative risk pDieMajor_FN vs. pDieMajor_TP (≥ 1)
pDieMajor_TN	Probability per year of dying from the major event state for a patient without disease and treatment N
pDieMajor_FP	Probability per year of dying from the major event state for a patient without disease and treatment P
RR_pDieMajor_FP	Relative risk pDieMajor_FP vs. pDieMajor_TN (≥ 1)
uMajorEvent	Utility per year in the major event state
RR_uMajorEvent	Relative risk uMajorEvent vs. uMinorEvent (≤ 1)
pDieOther	Probability per year to die of other causes (life-table used)
startAge	The mean age of examined patients

B Algorithm for EVPI calculation

1. For $i = 1, 2, \ldots, N$ simulations
   (a) Draw a value for θ
   (b) Calculate the expected net monetary benefit (NMB) of all strategies using this θ
   (c) Find the strategy which expected NMB is highest (this is the optimal strategy for this θ)
   (d) Subtract the expected NMB of baseline strategy a^* from the expected NMB of optimal strategy and record this number
2. Average these numbers over all N simulations

In formula form:

$$EVPI = \mathbb{E}_\theta[\max_a B(a,\theta) - B(a^*,\theta)]$$

C Algorithm for EVPPI calculation

1. For $i = 1, 2, \ldots, N$ simulations
   (a) Draw a value for θ_I
   (b) For $j = 1, 2, \ldots, M$ inner simulations
      i. Draw a value for θ_C
      ii. Calculate the expected net monetary benefit (NMB) of all strategies using this θ_I and θ_C and record these numbers
   (c) Average these numbers for all different strategies over all M inner simulations to derive the expected NMB for all strategies given θ_I
   (d) Find the strategy which expected NMB is highest (this is the optimal strategy for this θ_I)
   (e) Subtract the expected NMB of baseline strategy a^* from the expected NMB of optimal strategy and record this number
2. Average these numbers over all N simulations

In formula form:

$$EVPPI(\theta_I) = \mathbb{E}_{\theta_I}[\max_a \mathbb{E}_{\theta_C|\theta_I}[B(a,\theta) - B(a^*,\theta)]]$$

D Algorithm for EVPSI calculation

1. For $i = 1, 2, \ldots, N$ simulations
   (a) Draw a value for D
   (b) For $j = 1, 2, \ldots, M$ inner simulations
      i. Draw a value for θ_C and θ_I (out of the distribution of $\theta_I|D$)
      ii. Calculate the expected net monetary benefit (NMB) of all strategies using this θ_C and θ_I and record these numbers
   (c) Average these numbers for all different strategies over all M inner simulations to derive the expected NMB for all strategies given θ_I
   (d) Find the strategy which expected NMB is highest (this is the optimal strategy for this D)
   (e) Subtract the expected NMB of baseline strategy a^* from the expected NMB of optimal strategy and record this number
2. Average these numbers over all N simulations

In formula form:

$$EVPSI(\theta_I, n) = E_D[\max_a \mathbb{E}_{\theta_C, \theta_I|D}[B(a, \theta) - B(a^*, \theta)]]$$

E Model input Coronary Artery Disease

Parameter name	Distribution	Distribution-Parameters						Mean
cHC_RefTest	Log_Normal	logmean	8.006	logsdev	0.346			3186
cNHC_RefTest	Fixed Number		0					0
pMorbRefTest	Beta	alpha	145.112	beta	222408			0.001
cMorbRefTest	Log_Normal	logmean	8.808	logsdev	0.17			6787
disutilMorbRefTest	Triangular	min	0.022	likeliest	0.027	max	0.033	0.027
pMortRefTest	Beta	alpha	204.438	beta	222349			0.001

cHC_Test_A	Log_Normal	logmean	6.558	logsdev	0.18			716.5
cNHC_Test_A	Fixed Number		0					0
pMorbTest_A	Beta	alpha	1	beta	1999			0.001
cMorbTest_A	Log_Normal	logmean	8.808	logsdev	0.17			6787
disutilMorbTest_A	Triangular	min	0.022	likeliest	0.027	max	0.033	0.027
pMortTest_A	Fixed Number		0					0
pUninTest_A	Beta	alpha	1	beta	58			0.017
sensitivity_A	Beta	alpha	25	beta	0.3			0.988
specificity_A	Beta	alpha	7	beta	1			0.875

cHC_Treatm_P	Log_Normal	logmean	9.644	logsdev	0.16			15631
cNHC_Treatm_P	Fixed Number		0					0
pMorbTreatm_P	Beta	alpha	99.818	beta	1821.2			0.052
cMorbTreatm_P	Log_Normal	logmean	8.808	logsdev	0.17			6787
disutilMorbTreatm_P	Triangular	min	0.022	likeliest	0.027	max	0.033	0.027
pMortTreatm_P	Beta	alpha	21.325	beta	1725.5			0.012
pTreatmP_Minor_TP	Fixed Number		0					0
pTreatmP_Minor_FP	Fixed Number		0					0
pTreatmP_Major_TP	Fixed Number		0					0
pTreatmP_Major_FP	Fixed Number		0					0

cHC_Treatm_N	Fixed Number		0					0
cNHC_Treatm_N	Fixed Number		0					0
pMorbTreatm_N	Fixed Number		0					0
cMorbTreatm_N	Fixed Number		0					0
disutilMorbTreatm_N	Fixed Number		0					0
pMortTreatm_N	Fixed Number		0					0
pTreatmN_Minor_TN	Fixed Number		0					0
pTreatmN_Minor_FN	Fixed Number		1					1
pTreatmN_Major_TN	Fixed Number		0					0
pTreatmN_Major_FN	Fixed Number		0					0

pDisease	Beta	alpha	653	beta	267			0.71
discount_rate			2					
dt			1					
years_FU			15					
pDoRefTest_After_A			1					

Parameter name	Distribution	Distribution-Parameters						Mean
c_TP	Log_Normal	logmean	7.09	logsdev	0.649			1481
c_FN	Log_Normal	logmean	7.09	logsdev	0.649			1481
c_TN	Log_Normal	logmean	7.09	logsdev	0.649			1481
c_FP	Log_Normal	logmean	7.09	logsdev	0.649			1481
u_TP	Triangular	min	0.82	likeliest	0.87	max	0.92	0.87
u_FN		u_TP*RR_u_FN						0.696
RR_u_FN	Normal	mean	0.8	sdev	0.1			0.8
u_TN	Fixed Number		1					1
u_FP		u_TN*RR_u_FP						0
RR_u_FP	Fixed Number		0					0

cMinorEvent	Log_Normal	logmean	9.903	logsdev	0.4263			21902
pMinorEvent_TP	Beta	alpha	2	beta	98			0.02
pMinorEvent_FN		pMinorEvent_TP*RR_pMinorEvent_FN						0.05
RR_pMinorEvent_FN	Normal	mean	2.5	sdev	0.3			2.5
pMinorEvent_TN	Beta	alpha	1	beta	1000			0.001
pMinorEvent_FP		pMinorEvent_TN*RR_pMinorEvent_FP						0
RR_pMinorEvent_FP	Fixed Number		0					0
pDieMinorEvent_TP	Beta	alpha	5.5	beta	100			0.052
pDieMinorEvent_FN		pDieMinorEvent_TP*RR_pDieMinorEvent_FN						0.052
RR_pDieMinorEvent_FN	Normal	mean	1	sdev	0.1			1
pDieMinorEvent_TN	Beta	alpha	6	beta	100			0.057
pDieMinorEvent_FP		pDieMinorEvent_TN*RR_pDieMinorEvent_FP						0
RR_pDieMinorEvent_FP	Fixed Number		0					0
uMinorEvent	Triangular	min	0.742	likeliest	0.792	max	0.842	0.792

cMajorEvent	Log_Normal	logmean	10.309	logsdev	0.402			32526
pMajorEvent_TP	Beta	alpha	50	beta	50000			0.001
pMajorEvent_FN		pMajorEvent_TP*RR_pMajorEvent_FN						0.002
RR_pMajorEvent_FN	Normal	mean	2.5	sdev	0.3			2.5
pMajorEvent_TN	Beta	alpha	20	beta	50000			0
pMajorEvent_FP		pMajorEvent_TN*RR_pMajorEvent_FP						0
RR_pMajorEvent_FP	Fixed Number		0					0
pDieMajorEvent_TP	Beta	alpha	6	beta	90			0.063
pDieMajorEvent_FN		pDieMajorEvent_TP*RR_pDieMajorEvent_FN						0.063
RR_pDieMajorEvent_FN	Normal	mean	1	sdev	0.1			1
pDieMajorEvent_TN	Beta	alpha	6	beta	90			0.063
pDieMajorEvent_FP		pDieMajorEvent_TN*RR_pDieMajorEvent_FP						0
RR_pDieMajorEvent_FP	Fixed Number		0					0
pDieMajor_TP	Beta	alpha	42	beta	586			0.067
pDieMajor_FN		pDieMajor_TP*RR_pDieMajor_FN						0.167
RR_pDieMajor_FN	Normal	mean	2.5	sdev	0.3			2.5
pDieMajor_TN	Beta	alpha	42	beta	586			0.067
pDieMajor_FP		pDieMajor_TN*RR_pDieMajor_FP						0
RR_pDieMajor_FP	Fixed Number		0					0
uMajorEvent		uMinorEvent*RR_uMajorEvent						0.531
RR_uMajorEvent	Normal	mean	0.67	sdev	0.05			0.67

pDieOther								
startAge			62					

		outcomes attributes				
		1	2	3	...	n
weights		w_1	w_2	w_3	...	w_n
strategies	1	$u_{1,1}$	$u_{1,2}$	$u_{1,3}$	...	$u_{1,n}$
	2	$u_{2,1}$	$u_{2,2}$	$u_{2,3}$	...	$u_{2,n}$
	3	$u_{3,1}$	$u_{3,2}$	$u_{3,3}$	...	$u_{3,n}$
	⋮	⋮	⋮	⋮	⋱	⋮
	m	$u_{m,1}$	$u_{m,2}$	$u_{m,3}$	...	$u_{m,n}$

Table 3: Balance sheet

F Balance sheet example

Consider the following problem. There are m different strategies to be chosen from, and each strategy has got multiple (let say n) outcome attributes. Like effectiveness, safety, etc.... Each outcome is not a fixed number, but has an underlying distribution of the real parameter. The multiple outcomes also have got weights of importance. In the balance sheet (Table 3) you can see a tabular illustration. $u_{a,j}$ is the outcome of the j^{th} attribute of strategy a. Each outcome is a distribution, so for example $u_{a,j} \sim Beta(\alpha_{a,j}, \beta_{a,j})$ if this outcome has a beta distribution.

The problem is which strategy to choose. Or should we conclude that more research is needed, to make the right decision? And if more research is necessary, which outcome parameters have the highest value of information? In other words, which outcome attribute(s) should be further investigated?

Define $\theta = \{\theta_1, \ldots, \theta_m\}$ as the set of all outcome parameters, with $\theta_a = \{u_{a,1}, u_{a,2}, \ldots, u_{a,n}\}$. And define ω as the set of all weights ($\omega = \{w_1, \ldots, w_n\}$). The benefit of each strategy can then be written as a function of θ and ω

$$B(a, \theta_a, \omega) = \omega^T \cdot \theta_a = \sum_{j=1}^{n} w_j \cdot u_{a,j}$$

To derive the optimum decision we first calculate the expected value of perfect information (EVPI). The EVPI is the expected benefit if all parameter uncertainty will be eliminated. Such that all outcome attributes are exactly known, without an underlying distribution. It can be seen as the difference between the expected benefit of the optimum decision with perfect information minus the expected benefit of the optimum decision with current information. A strategy a without more information has an expected benefit of $\mathbb{E}_{\theta_a} B(a, \theta_a, \omega)$. So the expected benefit of the optimum decision with current information is $\max_a \mathbb{E}_{\theta_a} B(a, \theta_a, \omega)$. If the true parameters where known then the benefit of the optimum decision is $\max_a B(a, \theta_a, \omega)$. But because the true parameters are unknown we should average this expression over the joint distribution of θ and we get

$\mathbb{E}_\theta \max_a B(a,\theta_a,\omega)$ as the expected benefit of the optimum decision with perfect information. We derive the following formula for the EVPI:

$$EVPI = \mathbb{E}_\theta \max_a B(a,\theta_a,\omega) - \max_a \mathbb{E}_\theta B(a,\theta_a,\omega) \tag{4}$$

If the EVPI is low, then we expect that only a very low benefit will be gained with further research. So we will then choose the strategy with the greatest expected benefit. But if the EVPI is high we should consider whether to perform more research.

Next we should consider which outcome attribute(s) gives the most information. This can be done by calculating the expected value of perfect partial information. Suppose we have now perfect information of a subset of all parameters: $\theta_I \supset \theta$. And θ_C is the complement of θ_I. Now with perfect information of this subset θ_I the expected benefit of the optimum decision is given by $\max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta_a,\omega)$. But because the true parameters for θ_I are unknown we should average this expression over the joint distribution of θ_I and we get $\mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta_a,\omega)$ as the expected benefit of the optimum decision with perfect partial information. So we derive the following formula for the EVPPI:

$$EVPPI = \mathbb{E}_{\theta_I} \max_a \mathbb{E}_{\theta_C|\theta_I} B(a,\theta_a,\omega) - \max_a \mathbb{E}_\theta B(a,\theta_a,\omega) \tag{5}$$

By varying θ_I and calculating the EVPPIs we obtain information about which parameters provide the highest value when studied.

To eliminate all parameter uncertainty (of the subset) is impossible because this will require research study with infinite sample sizes. The EVPI and EVPPIs therefore give an upper bound of the expected benefit of doing further research. The larger the sample size, the closer the expected benefit will reach the upper bounds. In fact, the larger the sample size, the larger the reduction of the kurtosis (degree of peakedness) of the underlying parameter distributions (so reducing uncertainty). An additional factor is that the larger the sample size the higher the costs of the research. So a trade-off must be made between the costs and the expected benefit of doing the research.

After defining the most valuable parameters, data (D), for these set of parameters, could be obtain by doing the research. With this data we can update the underlying parameter distributions.

If the data is known the expected benefit of the optimum decision will be given by $\max_a \mathbb{E}_{\theta_C,(\theta_I|D)} B(a,\theta_a,\omega)$. But because the data is unknown we should average this expression over the joint distribution of obtaining data and we get $\mathbb{E}_D \max_a \mathbb{E}_{\theta_C,(\theta_I|D)} B(a,\theta_a,\omega)$ as the expected benefit of the optimum decision with partial sampling information. So we derive the following formula for the EVPSI:

$$EVPSI = \mathbb{E}_D \max_a \mathbb{E}_{\theta_C,(\theta_I|D)} B(a,\theta_a,\omega) - \max_a \mathbb{E}_\theta B(a,\theta_a,\omega) \tag{6}$$

If this EVPSI does exceed the cost of research, only then is further research justified.

G Treeage Model

CHOOSE

```
--- Costs
  c_FN=Dist(56)*dt
  c_FP=Dist(58)*dt
  c_TN=Dist(57)*dt
  c_TP=Dist(55)*dt
  cHC_RefTest=Dist(10)*dt
  cHC_Test_A=Dist(17)*dt
  cHC_Treatm_N=Dist(38)*dt
  cHC_Treatm_P=Dist(27)*dt
  cMajorEvent=Dist(81)*dt
  cMinorEvent=Dist(66)*dt
  cMorbRefTest=Dist(13)*dt
  cMorbTest_A=Dist(20)*dt
  cMorbTreatm_N=Dist(41)*dt
  cMorbTreatm_P=Dist(30)*dt
  cNHC_RefTest=Dist(11)*dt
  cNHC_Test_A=Dist(18)*dt
  cNHC_Treatm_N=Dist(39)*dt
  cNHC_Treatm_P=Dist(28)*dt
------
--- Other
  discount_rate=2*dt
  dt=1
  pDoRefTest_After_A=1
  startAge=62
  years_FU=15/dt
------
--- Probabilities
  pDieMajor_FN=pDieMajor_TP*RR_pDieMajor_FN
  pDieMajor_FP=pDieMajor_TN*RR_pDieMajor_FP
  pDieMajor_TN=RateToProb(ProbToRate(Dist(97),1),dt)
  pDieMajor_TP=RateToProb(ProbToRate(Dist(94),1),dt)
  pDieMajorEvent_FN=min(1,pDieMajorEvent_TP*RR_pDieMajorEvent_FN)
  pDieMajorEvent_FP=min(1,pDieMajorEvent_TN*RR_pDieMajorEvent_FP)
  pDieMajorEvent_TN=RateToProb(ProbToRate(Dist(91),1),dt)
  pDieMajorEvent_TP=RateToProb(ProbToRate(Dist(88),1),dt)
  pDieMinorEvent_FN=min(1,pDieMinorEvent_TP*RR_pDieMinorEvent_FN)
  pDieMinorEvent_FP=min(1,pDieMinorEvent_TN*RR_pDieMinorEvent_FP)
  pDieMinorEvent_TN=RateToProb(ProbToRate(Dist(76),1),dt)
  pDieMinorEvent_TP=RateToProb(ProbToRate(Dist(73),1),dt)
  pDieOther=tMort[startAge+Floor(_stage/dt)]
  pDisease=Dist(49)
  pMajorEvent_FN=min(1,pMajorEvent_TP*RR_pMajorEvent_FN)
  pMajorEvent_FP=min(1,pMajorEvent_TN*RR_pMajorEvent_FP)
  pMajorEvent_TN=RateToProb(ProbToRate(Dist(85),1),dt)
  pMajorEvent_TP=RateToProb(ProbToRate(Dist(82),1),dt)
  pMinorEvent_FN=min(1,pMinorEvent_TP*RR_pMinorEvent_FN)
  pMinorEvent_FP=min(1,pMinorEvent_TN*RR_pMinorEvent_FP)
  pMinorEvent_TN=RateToProb(ProbToRate(Dist(70),1),dt)
  pMinorEvent_TP=RateToProb(ProbToRate(Dist(67),1),dt)
  pMorbRefTest=Dist(12)
  pMorbTest_A=Dist(19)
  pMorbTreatm_N=Dist(40)
  pMorbTreatm_P=Dist(29)
  pMortRefTest=Dist(15)
  pMortTest_A=Dist(22)
  pMortTreatm_N=Dist(43)
  pMortTreatm_P=Dist(32)
  pTreatmN_Major_FN=RateToProb(ProbToRate(Dist(47),1),dt)
  pTreatmN_Major_TN=RateToProb(ProbToRate(Dist(46),1),dt)
  pTreatmN_Minor_FN=RateToProb(ProbToRate(Dist(45),1),dt)
  pTreatmN_Minor_TN=RateToProb(ProbToRate(Dist(44),1),dt)
  pTreatmP_Major_FP=RateToProb(ProbToRate(Dist(36),1),dt)
  pTreatmP_Major_TP=RateToProb(ProbToRate(Dist(35),1),dt)
  pTreatmP_Minor_FP=RateToProb(ProbToRate(Dist(34),1),dt)
  pTreatmP_Minor_TP=RateToProb(ProbToRate(Dist(33),1),dt)
  pUninTest_A=Dist(23)
  sensitivity_A=Dist(24)
  specificity_A=Dist(25)
------
--- Relative Risks
  RR_pDieMajor_FN=DistTrim(96,1,100)
  RR_pDieMajor_FP=DistTrim(99,1,100)
  RR_pDieMajorEvent_FN=DistTrim(90,1,100)
  RR_pDieMajorEvent_FP=DistTrim(93,1,100)
  RR_pDieMinorEvent_FN=DistTrim(75,1,100)
  RR_pDieMinorEvent_FP=DistTrim(78,1,100)
  RR_pMajorEvent_FN=DistTrim(84,1,100)
  RR_pMajorEvent_FP=DistTrim(87,1,100)
  RR_pMinorEvent_FN=DistTrim(69,1,100)
  RR_pMinorEvent_FP=DistTrim(72,1,100)
  RR_u_FN=DistTrim(61,0,1)
  RR_u_FP=DistTrim(64,0,1)
  RR_uMajorEvent=DistTrim(101,0,1)
------
--- Utility
  disutilMorbRefTest=Dist(14)
  disutilMorbTest_A=Dist(21)
  disutilMorbTreatm_N=Dist(42)
  disutilMorbTreatm_P=Dist(31)
  u_FN=u_TP*RR_u_FN
  u_FP=u_TN*RR_u_FP
  u_TN=Dist(62)
  u_TP=Dist(59)
  uMajorEvent=uMinorEvent*RR_uMajorEvent
  uMinorEvent=Dist(79)
------
pDiseaseNegativeTest=((1-sensitivity_A)*pDisease)/((1-sensitivity_A)*pDisease+specificity_A*(1-pDisease))
pDiseasePositiveTest=(sensitivity_A*pDisease)/(sensitivity_A*pDisease+(1-specificity_A)*(1-pDisease))
pTestPositive=sensitivity_A*pDisease+(1-specificity_A)*(1-pDisease)
Total_benefit=0
Total_cost=0
```

Figure 14: Reference test strategy