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A MONTE CARLO BASED SIMULATION NETWORK MODEL FOR A CHRONIC PROGRESSIVE DISEASE: THE CASE OF DIABETIC RETINOPATHY

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ABSTRACT

PROPHET (PROspective Population Health Event Tabulation) is an epidemiology-based network simulation program, written in Pascal, for modeling the progression of a chronic irreversible disease. It is designed to model multiple clinical and quality of life endpoints simultaneously. The program combines features of decision trees, Markov processes, and Monte Carlo simulation to produce a flexible and powerful micro-simulation tool.

Transition from one state to another is determined by a set of probabilities which are taken from population-based time dependent incidence rates. Tools have been developed to estimate incidence from prevalence where needed. Mortality is based on U.S. life tables and is adjusted for the additional risk imposed by one or more disease states. Alternative strategies for detecting and treating disease can be modeled in medical and economic terms. Net costs or savings are determined in each cycle and present value analysis is performed. Sensitivity analysis can be performed on any variable or group of variables. The benefit of screening and treatment can be assessed in terms of person-years of quality of life saved.

1. INTRODUCTION

Early detection and treatment are often the only effective means of reducing the morbidity and/or mortality of many chronic irreversible diseases. However, the costs of screening and treating these diseases can be substantial and decisions concerning screening strategies and targets are often made based on the costs involved and the benefits accrued. Although a variety of approaches to medical decision-making have evolved since Pauker's (1975; 1976; and 1980) original works with clinical decision trees, few have been proposed that adequately address the unique issues raised in modeling the course of a chronic irreversible eye disease. In conditions such as diabetic retinopathy, glaucoma, and macular degeneration, patients may be at risk for multiple ophthalmologic complications and may be eligible for more than one therapy. Individuals with chronic eye disease are frequently elderly and may have a greater mortality risk than non-diseased individuals of the same age (Podgor, Cosset, and Kannel, 1985). Furthermore, chronic eye diseases are generally bilateral, outcomes must be assessed in terms of the ultimate binocular vision of the patient.

1.1 Bayesian Decision-Tree Approaches

Previous investigators have attempted to model screening and treatment interventions in patients with glaucoma and ocular hypertension using Bayesian decision trees (Gottlieb, Schwartz, and Pauker, 1983; Eddy, Sanders, and Eddy, 1983). This approach, based upon Bayes Theorem, multiplies the probabilities at each branch of a tree in order to determine the net probability of any ultimate outcome. While this is the most commonly used decision-analytic tool for many applications and by far the simplest and fastest in terms of computational complexity, constraints of the model impose major limitations upon its usefulness in chronic eye diseases. The principal constraint is that every individual in the model must be assigned to an unique state to the exclusion of all other states. Thus, the model begins by a priori dividing patients into normals, ocular hypertensive, and glaucomatous individuals. This structure imposes difficulties in modeling individuals who move from one category to another or who can be assigned to more than one category at a time.

A second constraint of the tree approach is that the number of states increases geometrically as more

eventualities are added. In general, given n possible outcomes, the number of states necessary to include in a decision tree can be as many as 2^n. While this is a small portion of a much larger model, it is easy to see that the tree can rapidly become too complicated for ready comprehension by clinicians and others involved in the decision-making process to be a useful decision-making tool. This constraint becomes especially important in modeling eye diseases, because of the need to consider outcomes in each eye. Including the possibility of having an outcome in one or both eyes doubles the number of states for each outcome included. Examination of other recent real life applications of decision trees quickly reveals how quickly even simple conceptual models can become complex trees (England, Halls, and Hunt, 1989; Phelps and Phelps, 1989).

The third major constraint of Bayesian decision trees is their insensitivity to the passage of time. While this is not an issue in a short term decision, such as whether to operate on a patient who presents with abdominal pain, it limits the utility of the approach in modeling chronic eye diseases. Screening and treatment interventions in diseases such as diabetic retinopathy, glaucoma, and macular degenerations must be made over a period of years and the benefits of that intervention are similarly obtained over a prolonged interval. Additionally, during the course of the disease the patient is subject to risks of mortality and vision loss from other causes that may curtail the benefit of screening and treatment. Thus outcomes are most appropriately expressed in terms of "person-years" of benefit. Standard probability trees do not allow for this level of complexity.

1.2 The CAN*TROL Approach

The above limitations of Bayesian decision trees are widely recognized among cancer epidemiologists. Cancer, like many blinding eye diseases, follows a chronic course during which the patient is subject to multiple competing risks. In order to better model the effect of cancer screening and treatment strategies, the National Cancer Institute funded the development of CAN*TROL (Eddy, 1986a; Eddy, 1986b; Levin, Gait, and Kessler, et al., 1986). This modeling approach incorporates Markov processes to analyze the likelihood of state to state transitions during each passing time interval. Life expectancy is calculated by projecting each patient's passage through a series of health states to death. The Markov model is expressed via differential equations that must be solved mathematically.

While the CAN*TROL model is extremely useful in formulating cancer control strategies, it has limited applicability to eye disease. Under this model, living patients must be classified as either non-diseased or diagnosed with a particular stage of disease. All future events depend upon the initial disease state. The model does not allow for transitions from one disease state to another which is appropriate for cancer models, in which the initial staging of malignancy predicts all future events.

This is not the case in chronic eye disease. In the example of diabetic retinopathy, a valid model must allow for transition from background to proliferative disease. Future events can only be predicted based on the patient's current state, not the state at entry to the model. Allowing for these inter-state transitions in the CAN*TROL model would necessitate a major revision. Even if it could be accomplished, the model would still be limited by the fact that it can deal with only two outcome variables. Valid modeling of ophthalmologic diseases often requires that we incorporate multiple outcome variables, such as severe vision loss, reading vision loss, and mortality in the case of diabetic retinopathy.

1.3 The Coronary Heart Disease Policy Model

Weinstein and co-workers (Weinstein, Coxson, and Willams, et al., 1987; Goldman, Sia, and Cook, et al., 1988) have developed a decision-analytic model that does allow for state to state transitions. In constructing their model of coronary artery disease, they incorporated the risk factors associated with the underlying disease process in order to model the probability of moving from one risk-category to another. The model tracks risk factors for groups of individuals and applies known survival probabilities based upon those risk factors in each disease interval. The effects of preventive and therapeutic interventions can be studied in terms of prolonged survival and economic consequences.

Because the model deals with only one outcome variable (survival), groups of individuals can simply be allocated as living or dead based upon the probability of surviving each passing interval. If, however, multiple outcome variables are to be considered, a simple allocation cannot be made. Rather, individuals with exactly the same risk factors must be combined with individuals of like characteristics and considered as a group. When multiple risk factors for multiple outcomes are considered, this model quickly grows in complexity. The Weinstein model makes the simplifying assumption that risk factors have a fixed effect, regardless of disease duration. This assumption imposes substantial limitations in considering a condition such as diabetic retinopathy, where the annual risk of retinopathy increases with longer duration of disease.

1.4 The MISCAN Approach

Habbema and co-workers (1983), in their attempt to evaluate the effects of screening and treating chronic diseases such as cervical cancer, realized that simulations based on Markov processes lacked the sophistication to handle complicated situations which often occur in real life mass screening programs. To account for interrelations between factors and complex person level variables, Habbema developed MISCAN, a model based on the Monte Carlo simulation of individual life histories, to perform a "micro-simulation" of a cohort of individuals. Parkin (1985; 1986) used a similar approach to model cervical cancer screening programs in a single community instead of a cohort.

While these models begin to address the complexity found in chronic eye disease, they are still limited with regard to modeling multiple morbidity outcomes prior to death as well as taking into account the need to consider two eyes.

2. THE PROPHET SIMULATION SYSTEM

To address some of the limitations listed above we developed a computer program, PROPHET (PROspective Population Health Event Tabulation) to model chronic eye disease. The program was originally written in VMS Pascal and runs on a Digital Equipment Corporation VAX machine using the VMS Operating System. It has subsequently been ported to Sun and Sun-compatible workstations using the SunOS operating system and the Metaware Pascal compiler (Metaware Inc., Santa Cruz, CA).

PROPHET is similar to the Weinstein policy model in that it follows a cohort of individuals through a series of state transitions based on their underlying risk factors. While the Weinstein model deals with groups of patients in aggregate and assigns them to different outcomes in a deterministic manner, PROPHET uses the micro-simulation technique employed by MISCAN to model each patient as a separate individual. This allows for multiple outcome variables to be considered, along with the incorporation of duration-dependant risk factors.

PROPHET further differs from the Weinstein model in that the epidemiology and natural history of the underlying disease process is simulated as well as the effects of screening and treatment. Thus, the life expectancy and likelihood of ophthalmic complications change based upon age, duration of diabetes, level of retinopathy, and previous treatment.

In the PROPHET system, the course of a chronic irreversible disease is modeled as a multiple re-entry Markov process that is solved probabilistically rather than through the solution of closed-ended equations. The length of the time interval used in the model can be chosen according to the rate at which a particular disease is likely to progress.

2.1 Components of Model

All the individuals in the population being simulated start in one state, usually an undiseased or normal state, relative to the condition being studied. All members of the population can start at the same age (e. g., newborn) or the initial age distribution of the population can be specified. While alive, this population remains at risk of moving from the initial state to two other types of states. (1) A disease state is a condition which is not normal but which does not necessarily entail an increased risk of morbidity that would impact on quality of life. It may, however, be a prerequisite for progressing to a more advanced state of disease. It also has the potential of being screened for and treated if possible, which may have implications for progression to more serious conditions. (2) A sink state is a condition which results in a reduction in quality of life sufficient to warrant a change in lifestyle.

2.2 Simulation Technique

A random number generator is used to determine whether a person will progress from one state to another. For each state that a person is at three things must be determined: (1) the set of states that any individual could possibly progress to from that state; (2) of those states, which ones have not already been reached; and (3) the probability of progressing to those states. For each state to which a person could possibly progress, a random number between zero and one is generated and compared to the probability of progressing to that state. If the random number is less than that probability, then the person progresses to that disease. This process is repeated at predetermined intervals, usually monthly or annually.

This process is the same for disease states as well as sink states with one exception. The probability of progressing to a sink state is multiplied by a treatment factor before being compared to the random number. A treatment factor of one indicates that no treatment has been done or that it had no effect and a value of zero eliminates the possibility of progressing to the sink state. Values between zero and one lower the probability of progression to the sink state indicating the value of treatment.

There are three other special purpose states. A treatment state is used to indicate if a person has received a particular treatment. A death state is a sink

state that overrides all others and eliminate the individual from future cycles of simulation. A screening state describes various parameters associated with particular screening methods.

A list of probabilistic equations is shown in Appendix C which indicate the various factors which are combined to determine an event.

2.3 Initial Conditions

Before the simulation can begin, the program must be given a number of items of information. This information is used to form a structure known as a network. Each state is called a node in the network and a directed path between two nodes is used to illustrate the possibility of progressing from one state to another. The information required by the program is divided into two sets, one which describes each node, and one which describes the paths between the nodes. These two data sets are described in Appendix A and B, respectively.

Additionally, some information is gathered interactively from the user before each execution of the program. This includes information about the names of input and output files as well as other runtime parameters. These variables are also described at the end of Appendix B.

2.4 Mortality

At the beginning of each cycle, before any determinations are made concerning disease progression, the individual enters the lifetable module. The probability of death is compared to a random number as with disease progression and a death results in removal from the simulation. The probability of death can be specified in several ways. In the absence of information, U.S. life tables are used to determine the age-specific probability of death (U.S. DHHS, 1984). In addition, if a certain state carries with it a relative risk of death above the average population, that risk can be applied to the life table probability. If desired, the life table probability can be overridden with a specified probability which is constant for all ages. Since the relative risk approach may tend to overestimate mortality at older ages when mortality is high anyway, and since a constant risk may underestimate mortality at older ages for the same reason, these two values can be used together and an average of the two probabilities used. Since adjustments to the life table probability are specific to a particular state, if a person is at more than one state the maximum probability of death for those states is taken.

2.4 Screening

The presence of many chronic conditions can only be determined by a physical examination and/or diagnostic tests. Hence, it is important to keep track not only of disease progression but also of whether the progression is detected by the person and/or their caregiver. At the beginning of each cycle the program determines if a screening visit is being performed during the interval. This is based on the specified screening frequency for each state. If an individual is at more than one state that person will be screened based on the state with the most frequent screening visits. It may also be desirable to delay screening for a specific amount of time based on the knowledge that the disease only progresses after a period of latency. In some cases, it may also be necessary to specify that a certain proportion of the population may never be screened and will never have disease detected.

In some cases, it is possible that the screening test will yield a false negative result. In this case the screening test will fail to detect the presence of disease. Thus, disease progression is detected in a given interval if a screening visit is performed and the visit resulted in the detection of disease. The false negative rate is specified in terms of the sensitivity of the test, that is, the probability of detecting disease when it, in fact, is present.

Conversely, it is possible that the screening test will yield a false positive result which can lead to unnecessary tests and even treatment. The false positive rate is specified in terms of the specificity of the test, that is, the probability of detecting disease when it, in fact, is not present.

To make the implementation of features dealing with sensitivity and specificity more appropriate we have also added the ability to perform confirmatory screening tests based on the results of the initial test. Commonly, these tests have better sensitivity and/or specificity and are more costly to perform. Thus, we can simulate the real life situation of incurring extra costs as a result of the deficiencies in the screening method used.

2.5 Treatment

If a person has a treatable disease a number of conditions must be fulfilled before the treatment can take place.

First, the disease must be known. As noted above, a screening visit must take place and the disease diagnosed before the disease can be known. Second, the person cannot already have reached a sink state with regard to that disease. Third, the person must have a screening visit in an interval in which they are eligible for treatment. Thus, a person who progresses to a disease between screening visits cannot be treated until the screening visit at which the disease is detected,

provided, of course, that they are still eligible for treatment (i.e., they have not reached a sink state in the meantime). Fourth, the person must accept the treatment. There may be a proportion of the population who will refuse treatment even if they are eligible in all other respects. This can be applied in one of two ways. The program can identify that segment of the population which will never receive treatment for as long as they are eligible. Alternatively, at each visit a proportion of those eligible for treatment will not receive treatment but will remain eligible for treatment at subsequent visits. Fifth, the person cannot already have been treated for the disease.

If the person satisfies all of the conditions they receive a "treatment factor" which will provide some protection against subsequent progression to a sink state. The factor is derived from the probability of successful treatment as determined in treatment trials. If the treatment is applied to both organs in a two-organ system (e.g., eyes, ears, lungs, kidneys, etc .) a correlation factor can also be specified which determines the probability of successful treatment in one organ given the result of the treatment in the other. From this the probability of a successful treatment in at least one of the organs, which then becomes the treatment factor, can be calculated (Appendix C).

2.6 Costs

If a person has a screening visit during a given time interval the cost of that visit is computed. If the cost of a screening visit is different depending on the state, the maximum cost of any screening visit that a person can have is used. If more than one visit occurs during a time interval the charge is applied the appropriate number of times. The total charges for each person in the simulation are added together to get a total screening cost.

The cost of each screening episode can be specified as a constant cost or it can be a function of the screening coverage. Often, even though the actual cost of the test is constant, efforts to increase coverage will result in a proportionate increase in the cost per screening test. We can also specify that a certain proportion of the population will never be screened by using this feature.

If a person is treated for a disease during a time interval the cost associated with that treatment is computed and added to the total treatment cost for the whole simulation.

2.8 Benefits

Benefits are computed by determining if treatment was effective in preventing or putting off progression to a sink state. Since a sink state can be thought of as a loss of quality of life, effective treatment can be said to save quality of life. Each year that a person spends in a sink state is known as a "person-year of quality of life lost" (PYQLL) and each year in which treatment is preventing a person from progressing to a sink state is known as a "person year of quality of life saved" (PYQLS). PYQLL is determined by adding up all the years that each person spends in a given sink state. In order to compute PYQLS we must first compute the "person-years of quality of life that would have been lost had it not been for treatment" (PYQWL). The likelihood of progressing to a sink state in a given interval depends both on the probability of progression and on the effectiveness of treatment. If we use just the probability of progression without taking into account treatment we can see what would have happened without treatment. Each year in which we can determine that a person would have progressed to a sink state had they not received treatment we add a year to the PYQWL. PYQLS, then, is the difference, PYQWL minus PYQLL. This quantity can be determined for each disease, treatment and sink of interest.

2.9 Cost-Effectiveness Analysis

In order to compare the costs of screening and treating a disease with its benefits we need to know the cost of a PYQLL. This can be the cost of a year of disability, the cost of hospital care or any other cost associated with loss of quality of life. Since these costs are often associated with loss of earnings, three costs can be specified, one for each age group 0-18, 18-64, and 65+. We can then turn this around to say that a PYQLS results in the savings of the cost of a PYQLL and is thus a benefit. Each year the cost of screening and treatment for that year is subtracted from the savings resulting from the total PYQLS for that year. This is the net benefit. The net benefits from each year are then added up to get the total benefit. Net benefits are expressed in terms of their present value. This analysis is performed as suggested by Weinstein and Stason (1977; 1986) to adjust for the relative value of dollars spent now, as compared with benefits to be regained in the future. Bradford (1983) has suggested that the appropriate discount rate for a government investment must consider not only preference for money, but the reduction in private capital caused by an increase in government spending. Most analyses using the PROPHET modeling system employ a discount rate of 5%, which is commonly used in similar analyses (Weinstein and Stason, 1982; Doubilet, Mcneil, and Weinstein, 1985). As seen below, however, this rate can be varied to

assess its impact on the model's predictions.

2.10 Sensitivity Analysis

Having established appropriate values for costs, benefits, and net benefit, we can look at the effect of changing certain parameters on these values. If desired, the user can specify a range of values for any parameter in the Network Node Definition file or any probability in the Network Path Definition file. The simulation is then run for specific increments within the range, the size of the increments determined by the number of times the simulation is run. With this information one can then analyze the effect of varying a particular parameter on outcomes of interest, for example, PYQLS, Costs, and Present Value.

2.11 Variance Analysis

Since the simulation is based on random number generation and each simulation starts with a different random number seed (except for sensitivity analysis, where the seed is held constant and the same sequence of random numbers is generated for all simulations within a single run) the results from a series of individual runs will be different. Comparing results from these runs we can determine the variance introduced by random variation in the random number generator. Clearly, increasing the size of the population simulated and doing more simulations will lower the variance. However, available computer resources may limit this ability so it is desirable to determine the variance given limitations on computer resources.

It is also apparent that there could be substantial variance introduced by variation in the individual parameters used due to epidemiologic uncertainty. To determine the effect of sample variation in the parameters we can specify a variance for each parameter and each time the simulation is run values for the parameters are chosen from a normal distribution with the given mean and variance. Multiple runs done in this fashion will indicate the effect of sample variation on the results of the simulation.

3. CONCLUSION

The PROPHET simulation system is a flexible yet powerful program for modeling the progression of multiple clinical and economic outcomes within the course of a chronic irreversible disease. Its application to the ocular complications of Type I diabetes has been described elsewhere (Javitt, Canner, and Sommer, 1989; Javitt, Canner, and Frank, et al., 1990). Although it was specifically designed to model chronic eye disease it may also be useful for modeling other human organ systems which come in pairs, such as lungs, kidneys, limbs, etc. Thus, for example, this model could also be employed to examine the effects of kidney disease secondary to diabetes. The paired-organ feature, however, can also be bypassed for more general chronic conditions. Additionally, this system would be useful to model any disease which has secondary clinical morbidity which presents before the primary morbidity or mortality of the disease have been manifest. For example, the disease AIDS has as part of its clinical spectrum many non-fatal events which have significant clinical and economic significance well in advance of the premature mortality common in those with AIDS.

We look forward to applying this model to other chronic diseases as the appropriate epidemiologic and treatment data become available.

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Appendix A: List of Variables Required for PROPHET Node Definition

The following variable are included for each state:

Variable Name	Variable Definition
ID	Unique number for node
NAME	Node description
STYPE	Node type: DISEASE, SINK, TREATMENT, DEATH, SCREENING

The following variables are included if STYPE is DISEASE:

REFNODE	ID of reference node:
INITSCREEN	ID of initial screening method
NUMDELAYPT	Number of ordered pairs that make up the screening delay function as specified below
PDELAY	Proportion of people who will experience the following screening delay
SCREENDELAY	Number of months from onset

	of disease to screening
SCREENINTER	Number of months between screening visits
RR	Relative risk of death for this node

The following variables are included if STYPE is TREATMENT:

TRTD	ID of DISEASE node being treated
TRTS	ID of SINK node that being treated will prevent
PEFF	Treatment efficacy, expressed as a probability
PCORR	Correlation (Range -1:1) between treatment outcomes in a two organ system (always 1 if one organ)
PCOVER	Treatment Coverage: Percentage of population who will accept treatment
TRTPRICE	Cost of treatment
UNNEC_STATE	ID of state that patient will proceed to if treatment is performed unnecessarily
UNNEC_PROB	Probability of proceeding to UNNEC STAT if treatment is performed unnecessarily
SIDEFF_STATE	ID of state that patient will proceed to if treatment causes adverse side effects
SIDEFF_PROB	Probability of proceeding to SIDEFF STATE if treatment causes adverse side effects

The following variables are included if STYPE is SINK:

REFNODE	ID of DISEASE node that led to progression to this node
RR	Relative Risk of death for this node
COST_PYQLL(3)	Cost of a Person-Year of Quality of Life Lost: used to establish benefit of saving a PersonYear of Quality of Life. Three values can be specified for age groups 0-18, 18-64, and 65+

The following variables are included if STYPE is SCREENING:

NUMCOVPT	Number of ordered pairs that make up the coverage-cost function as specified below
COVERAGE	Proportion of people who will be screened at the given cost
COST	Cost of a screening visit
SENS	Sensitivity of screening exam
SPEC	Specificity of screening exam
CONFIRM	ID of SCREENING node to use to confirm screening result

The following variable is the same regardless of the state:

DISC_RATE	Discount rate for discounting net benefits in future years

The following variables are not in the node definition file but are input at the beginning of each run:

TIMEUNITS	Number of time intervals per year
MAXTIME	Number of years to run
MAXSIM	Number of simulations to run

Appendix B: Structure of Network Path Definition File

The following set of variables is repeated for each path:

Variable Name	Variable Description
STARTNODE	Starting node of path
ENDNODE	Ending node of path
P	Annual probability of transition across path
TIME	Number of years since arrival at REFNODE to which the probability is to be applied. This can be single time point or a range.
VARIANCE (Opt.)	The variance associated with the probability specified. This can be used to run a series of models to determine the variance associated with the input parameters

These variables are stored in a three-dimensional array whose elements are the probabilities (P) and whose indices are STARTNODE, ENDNODE, and TIME.

The time index is arranged in single year increments so if TIME is specified as a range, each year in the range is given an element in the array.

Appendix C: Probabilistic Equations

Pr{ One person-year of sight saved during interval i} =

Pr{ (Having PDR at i-1) AND (NOT Progressing from PDR to blindness) AND (Treatment performed) AND (Treatment effective) } =

Pr{ PDR at i-1 } * Pr{ NOT progressing } * Pr{ Treated } * Pr{ Effective }

where
Pr{ PDR at i }= { (Having PDR at i-1) OR ((Having BDR at i-1) AND (Progressing from BDR to PDR)) } =
Pr{ PDR at i-1} + Pr{ BDR at i-1 } * Pr { Progressing }

Pr (BDR at i } ={ (Having BDR at i-1) OR ((Having IDDM at i-1) AND (Progressing from IDDM to BDR)) } =
Pr{ BDR at i-1) + Pr{ IDDM at i-1 } * Pr { Progressing }

Pr{ NOT progressing from PDR to blindness }= 1-Pr{ Progressing}

Pr{ Progressing from IDDM to BDR } =P[IDDM,BDR,Time since IDDM] Pr{ Progressing from BDR to PDR } =P[BDR,PDR,Time since IDDM] Pr{ Progressing from PDR to blind } =P[PDR,Blind,Time since PDR]

Pr{ Treatment performed } =Pr{ (Disease is known) AND (NOT blind) AND (Agrees to be treated) } =
Pr{ Disease is known } * Pr{ NOT blind} * Pr{ Agrees to be treated}

Pr{ Disease is known } =Pr{ Detecting disease | Disease exists } * Pr { Screened in i }

Pr{ Detecting disease | Disease exists } =SENS

Pr{ Screened in i } =Pr { No screen delay } * Pr { Screening visit interval falls in i } * Pr { Cost of screening is not prohibitive }

Pr{ No screen delay } ={ 1 if time since onset > SCREENDELAY
{ 0 if time since onset <= SCREENDELAY

Pr{ Screening interval falls in i }=
{ 1 if elapsed time MOD visits_per timeunit= 0 or if visit_per timeunit<1
{ 0 else
visits_per timeunit= SCREENINTER*TIMEUNITS/12

Pr{ Cost of screening not prohibitive } ={ 1 if cost < $999.99
{ 0 else

Pr{ NOT blind at i } =1 -Pr{ Blind at i }
Pr{ Blind } =Pr{ (Blind at i-1) OR ((PDR at i-1) AND (Progressed from PDR to blindness)) }

Pr{ Treatment effective }=
Pr{ Preventing progression to sink state in at least one organ}= Pr{ Preventing progression to sink state in only one organ }*2 + Pr{ Preventing progression to sink state in both organs }

Pr{ Preventing progression to sink state in both organs }= PEFF * (PCORR*(1-PEFF) + PEFF)

Pr{ Preventing progression to sink state in only one organ } = PEFF -Pr{ Preventing progression in both organs }

Pr{ Agrees to be treated } =PCOVER

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