Table of Recommendations:

1. The modeling team should consult widely with subject experts and stakeholders to assure that the model represents disease processes appropriately and adequately addresses the decision problem.

2. A clear, written statement of the decision problem, modeling objective, and scope of the model should be developed. This should include: the spectrum of disease considered, perspective of the analysis, target population, alternative interventions, health and other outcomes, and time horizon.

2.1. The scope and structure of the model should be consistent with, and adequate to address, the decision problem/objective and the policy context.

2.2. The perspective of the analysis should be stated and defined. Outcomes modeled in the analysis should be consistent with the stated perspective. Analyses which take a perspective narrower than the societal perspective should report which outcomes are included and which are excluded.

2.3. The target population should be defined in terms of geography, patient characteristics (including co-morbid conditions), and disease stage, each of which should be appropriate to the decision problem.

2.4. Health outcomes modeled in the analysis, which may be measured as events, cases of disease, deaths, quality-adjusted life-years, disability-adjusted life-years, or other measures important to decision makers and stakeholders, should be directly relevant to the question being asked.

2.5. Interventions or strategies modeled in the analysis should be clearly defined in terms of frequency, component services (including services that may have preceded the intervention and that would affect its course), dose or intensity, duration, and any variations required for target subgroups.
3. Although data are an essential component of a model, the conceptual structure of a model should be driven by the decision problem or research question and not determined by data availability.

3.1. The choice of strategies/comparators crucially affects results, and should be determined by the decision problem and not by data availability or quality. All feasible and practical strategies should be considered. Constraining the range of strategies should be justified.

3.2. The time horizon of the model should be long enough to capture relevant differences in outcomes across strategies. A lifetime time horizon may be required.

4. The conceptual representation of the decision problem should be used to identify key uncertainties in model structure where sensitivity analyses could inform the impact of structural choices. For example, where a lifetime horizon is used, the impact of alternative methods of extrapolating beyond the observed data should be explored.

5. The policy context of the model should be clearly stated. This includes who funded the model, who developed the model, whether the model was developed for a single application or multiple potential application, and who the policy audience for the modeling work is.

6. An explicit process (expert consultations, influence diagrams, concept mapping, or similar method) should be used to convert the conceptualization of the problem into an appropriate model structure to ensure that the model reflects current theory of disease or the process being modeled.

7. There are often several types of models that are suitable for the decision problem, and versions of each of the three modeling types in the series can be used for the same decision problem. Some problems are more naturally represented in certain modeling types than in others.

7.1. For relatively simple models, or decision problems with special characteristics (e.g. very short time horizons, complex value structures) a decision tree may be appropriate.

7.2. If the conceptualization involves representing the disease or treatment process as a series of health states, state-transition models are often appropriate as they may be simple to develop, debug, communicate, analyze and readily accommodate the evaluation of parameter uncertainty. Their primary disadvantage, the Markovian assumption that transition probabilities do not depend on past history, can be addressed by increasing the number of states. Individual-based state-transition models (termed microsimulations), which do not require this assumption, are an alternative when the number of states grows too large.

7.3. When the disease or treatment process includes interactions between individuals, the modeling methods should be able to represent and evaluate the effects of those interactions (Dynamic transmission models, discrete event simulation models, agent-based models).

7.4. When the decision problem involves resource constraints, the modeling method should be able to represent and evaluate the effects of those constraints (discrete event simulation, agent-based models).
7.5. For some decision problems, combinations of model types, hybrid models, and other modeling methodologies are appropriate.

8. Model simplicity is desirable for transparency, ease of validation and description. However, the model should be sufficiently complex to answer the question at a level of detail consistent with the problem being modeled, and to preserve face validity to clinical experts. Greater complexity may be necessary in policy models that are intended to be used for many decision problems.
Section 1: Introduction

The purpose of this paper is to summarize good research practices regarding the development of a model from the conceptualization of the problem that the model is expected to inform, through the representation of the disease or health care processes of concern in the form of a decision model. The ISPOR Task Force of Good Research Practices has accepted that in this context, the purpose of a model is to inform medical decision making and health-related resource allocation questions. This conceptualization originated from the boundaries defined the ISPOR Task Force on Good Research Practices in Modeling Studies.1 Specifically, we restrict our attention to models as normative aids to decision making. Our recommendations apply most directly to models whose explicit purpose is to structure evidence on clinical and economic outcomes in a form that can help decision makers to choose from among competing courses of action and to allocate limited resources in health and medicine. This restriction is important because we do not consider the conceptualization of all modeling types, but rather the more limited set used for decision making in health.

Perhaps no other word in the policy analyst’s lexicon inspires greater confusion among lay observers than model. Most would agree that a model is a simplified representation of reality. Beyond that description, the word “model” may lead in any number of directions. The defined purpose of this paper excludes from consideration a large number of useful, scientifically sound forms of modeling. For example, statistical regression models lie outside the scope of this report. While regression is of critical importance in generating input data for decision models, it is a descriptive method. The aim of regression is to explain and predict the relationship between inputs and outputs. A regression model, however, cannot give normative direction between two policy options, and is therefore not considered here. A dynamic, infectious disease transmission model is probably beyond the scope of this report if it restricts attention to what epidemics do to people; but it is probably within the scope of this report if it uses that information to evaluate what people can potentially do to affect epidemics. For the purpose of this series of papers, we offer guidance only for models that are used to directly inform decision making. Figure 1 describes the basic structure of the modeling process as developed by the task force. This paper describes two distinct components of the modeling process: the conceptualization of the problem, which is designed to convert the knowledge of the health care process or decision into a representation of the problem, followed by the conceptualization of the model, in which the components of the problem are represented using a particular analytic method. (1 in the figure) The conceptual representation of the model will usually direct the decision as to the type of modeling technique to be used (2, 3, 4 in the figure), three common methods of which are described in accompanying papers.2-4 The current paper covers the modeling process up to the selection of model type; best practices for particular model types are discussed in the specific modeling methods papers, and the data that is used to calibrate it and the inherent uncertainty of model representations is discussed in the paper in this series on calibration and uncertainty.5 One of the most important consequences of the process of explicitly conceptualizing the model is that this can then be used to structure the transparency of the presentation and the testing of the validity of the model, which are the topic of the final paper in this series.6

Section 2. Conceptualization of the Problem
Statement of the decision problem and objective

Before constructing a model, it is important to be clear about the nature of the general problem under consideration, and the objectives of the modeling project. The broad objective of constructing a model must be identified at the outset, and will usually fall within one of several categories. Models can be constructed to:

**Guide clinical practice.** Example: Mandelblatt et al. described a modeling exercise involving 6 simulation models designed to support the recommendations of the US Public Health Services Task Force on mammography screening. This study will be used as ongoing example for how the objectives, scope, and policy context of a modeling exercise can be described (see Box).

**Inform a funding decision for a new drug, device, or program.** Example: Wijeysundera et al. evaluated the cost effectiveness of multidisciplinary heart failure clinics in order to guide the decision of the Ontario Health Technology Advisory Committee regarding widespread diffusion of heart failure clinics in Ontario.

**Optimize use of scarce resources (e.g. organs for transplantation, beds in the emergency room).** Example: Schechter et al. developed a model of the organ allocation system in the US to guide policy around optimal use of a scarce resource (livers available for transplantation).

**Guide public health practice (e.g. antiviral use or school closures for influenza pandemics.** Example: Sander et al. evaluated the cost effectiveness of universal vaccination for epidemic influenza.

The nature of the decision problem will have important implications for model structure, data requirements, analytic strategy, and reporting. Components of the decision problem, including factors such as disease or condition, patient or study populations, possible diagnostic or therapeutic actions and interventions, and possible outcomes, will be clearly addressed in the scope of the modeling project (discussed further in SECTION 2.b).

Although the general nature of the problem may be clear at the outset, there is often some degree of ambiguity leading to variation in how the problem is understood by stakeholders. For example, Paulden et al. developed a model to evaluate Oncotype DX, a genetic test that aids in patient selection for adjuvant therapy for breast cancer. While it was clear that the purpose of model development was to inform a policy decision about whether the test should be covered, it subsequently became apparent that the problem could potentially be understood in several ways. One way of conceptualizing the problem was to ask what the consequences of a positive decision were likely to be, in practice, with respect to health outcomes and costs. A model answering this question would represent current or projected practice with respect to clinical risk stratification, use of the new test, and use of chemotherapy conditional on test results. The potential benefits of testing are then compared to current practice. A second way of framing the problem is to ask about the circumstances under which the use of Oncotype Dx might be optimal. A model answering this question must explore potential benefits of testing in a wide variety of risk groups, and a wide variety of treatment options conditional on test results, irrespective of how the test is currently used in practice.
An early attempt to specify the precise nature of the decision problem and modeling objectives is likely to improve the efficiency of the model building task. Defining the modeling objective is likely to be an iterative process, and specific objectives may change as understanding of the decision problem deepens over time.

The remainder of this paper details each of the task force recommendations, and provides explanation and rationale. Task force Recommendations are repeated in **bold**.

1. **The modeling team should consult widely with subject experts and stakeholders to assure that the model represents disease processes appropriately and adequately addresses the decision problem.**

   It is important to read and consult widely, and refine the policy or decision problem, to the extent possible, early in the process of model development. Existing models addressing the same or related decision problems should be reviewed carefully. The clinical and policy literature describing the problem should be understood by the modeling team. Experts, including clinical, epidemiologic, policy, and methods experts should be consulted. The role of clinical experts in developing a representation of clinical practice problems is central. Policy experts, should be consulted when the model is intended to address a clinical or health policy decision (e.g., funding a new drug or program). Consultations with patients, individually, or by means of patient groups, may deepen understanding of the values and preferences relevant to the decision problem.

2. **A clear, written statement of the decision problem, modeling objective, and scope of the model should be developed. This should include: the spectrum of disease considered, perspective of the analysis, target population, alternative interventions, health and other outcomes, and time horizon.**

   It is very useful to create a written statement of the decision problem early in the process of model formulation. Ramwadhdoebbe suggests: “The process of creating a narrative description of the problem lets the problem stakeholders and decision makers provide direct input into the model. ... Once complete, the narrative ... serves as a reference point for further discussion and refining the problem description.” The process of creating a problem statement may uncover variations in the way in which stakeholders conceptualize the decision problem, and aid the development of a clear, shared, modeling objective(s).

   In addition to a general statement about the nature of the decision problem (Should Oncotype DX be funded in the Ontario health care system?), a problem statement should also include a statement of the objective of the modeling project (What are the aggregate health effects, net costs, and cost effectiveness of Oncotype DX, if used optimally within the Ontario health system?).

   To build a model the analyst must choose an analytical structure appropriate for the decision problem and identify data to populate it. Thus the next step is to make the decision problem more specific. The appropriate perspective must be carefully defined, as must the target population, the health outcomes of importance for that population, the technologies/settings to be considered for addressing the disease, whether and how costs will be represented, and the time horizon over which all outcomes (health outcomes, events, costs predicted by the model) will be projected.
The experts and stakeholders who helped frame the decision problem need to be involved in helping to define the specifications of the model. The development of a statement characterizing model objectives and specifications can usually be done simultaneously.

2.1. The scope and structure of the model should be consistent with, and adequate to address, the decision problem/objective and the policy context.

The disease or condition specified in the decision problem plays a critical part in determining which interventions and health outcomes are relevant to the decision problem. Typically, a single disease (e.g., breast cancer) or set of closely related diseases (e.g., cardiac, cerebrovascular, and peripheral vascular disease) is of interest. Other diseases may be included if they are sequellae of the disease of interest or they are common comorbidities that affect its course. The decision problem, and thus the model, can, however, encompass a broad range of diseases or conditions. For example, Statistics Canada maintains a population health model that simulates the effects of risk factors such as smoking and weight on the development and course of a wide range of diseases including osteoarthritis, cancer, diabetes and heart disease.\(^\text{16}\)

The availability of data is likely to constrain the development of the model, but the initial discussion of how to make the decision problem more specific should range broadly and encompass features of the disease and its outcomes for which data may be poor or unavailable. It is important to have a complete picture of the decision problem, regardless of data availability. It is also often possible to conduct sensitivity analyses on model features for which no data exist in order to investigate their influence on the results. For example, the breast cancer screening models used in the USPSTF modeling exercise\(^\text{7}\) include a component that represents the unobserved pre-clinical stages of breast cancer. Various methods are available for inferring possible values for unobserved model parameters.\(^\text{17}\)

2.2. The perspective of the analysis should be stated and defined. Outcomes modeled in the analysis should be consistent with the stated perspective. Analyses which take a perspective narrower than the societal perspective should report which outcomes are included and which are excluded.

Perspectives commonly considered are those of the patient, of the health plan or insurer, and of society. In some cases the perspective of employer (responsible for health insurance premiums and interested in workforce productivity) may be important. The Panel on Cost-Effectiveness in Health and Medicine recommended the societal, or public interest, perspective.\(^\text{18}\) This includes all significant health outcomes and costs, no matter who experiences the health outcomes or pays the costs, and no matter whether the costs are matched by budgetary outlays or provided without payment. Perhaps because of the Panel’s recommendation analysts sometimes assert that their study uses the societal perspective, even when the outcomes and costs included are those of a somewhat narrower (‘health care payer’) perspective.\(^\text{19}\)

When a model simulates health and disease without assigning costs, the perspective of the analysis – “Whose health effects matter” – is typically left unstated. Most commonly, models focus on the health outcomes that accrue to patients who have, or are at risk of, the disease of interest and who receive the interventions represented in the model. Effects on the health of others, if any, are not included. Although widely used, this perspective has never been explicitly defined or
named; we will call it the clinical or medical sector perspective. This perspective is closest to that of clinical decision making, in which health outcomes associated with different treatment options for the presenting patient (only) is considered, based on evidence for cohorts of patients with similar characteristics.

When costs are included in an analysis, modelers have long recognized the need to state a perspective explicitly: “Whose costs are to be counted?” Because the perspective specifically for health outcomes has traditionally been left unstated, it is less often recognized that all model outputs, that is health outcomes and costs, should be analyzed from the same perspective. In practice, the great majority of modeling studies adopt the medical sector perspective for both health effects and costs, a perspective conventionally described, a bit inaccurately, as the health care payer perspective. The health care payer perspective includes only those health outcomes that accrue to the patients who receive the interventions being modeled. Costs included are the full costs paid for the medical services required to provide the intervention. These differ from costs to a health plan or insurer if patients are responsible for co-pays and co-insurance.

Resources provided without payment, such as the time of volunteers or family members, and the time of patients themselves, as well as costs incurred outside the medical sector are not included.

The evaluation of mammography undertaken for the USPSTF stated that it adopted the societal perspective (Box), but the outcomes modeled suggest that the perspective might be better described as the medical sector perspective. The evaluation modeled breast cancer outcomes for the target population, but limited costs to counts of mammograms and unnecessary biopsies, in keeping with the Task Force’s charge to base recommendations only on medical effectiveness.

Choice of perspective, and the care with which the perspective is carried through, is a source of variation within and across studies. Its impact on the results of a study could be explored through sensitivity analysis, but, whether or not this is done, it is important to be accurate in describing and correctly applying the chosen perspective.

2.3. The target population should be defined in terms of geography, patient characteristics (including co-morbid conditions), and disease stage, each of which should be appropriate to the decision problem.

The target population is the population that has, or might develop, the disease(s) and that will receive the interventions being modeled. The population is also defined by geography, as the population living in a specific community, country, or group of countries. The stage of the disease and the timing of or route of access to the intervention often affects the definition. A vaccination to be delivered to children necessarily implies that the target population is children, but the options can be more complex. An evaluation of rubella vaccine, for example, considered the vaccination of children or women of childbearing age, and therefore had two rather different possible target populations (Knox 1980).

Mammography screening is considered only for women 40 or older, so the target population for the USPSTF evaluation was US women 40 and older (Box).

In some cases populations that are not the target of the intervention(s) will be affected by it. The obvious example is vaccinations, which often confer benefits (herd immunity) on unvaccinated people (Kim and Goldie 2008). Folic acid fortification of grains aims to prevent neural tube defects in infants, but may harm the elderly (Kelly 1996). Health outcomes and the consequences of introducing new health care interventions may confer (or in some cases reduce) substantial responsibilities on the families and friends of patients, which can generate costs, and which can also affect their
health. For problems involving groups receiving care from family members (children, the elderly, the disabled) – where the disease strongly affects others, consideration should be given to the effects of health interventions on costs and health.

The target population may need to be classified into subgroups to reflect characteristics that affect the course of disease, the impact of the intervention, and thereby the costs and other outcomes of the model. These characteristics may include age, prior course of disease, health behaviors, comorbidities, and genetic predisposition or family history. The variety and levels of these characteristics can affect the choice of model (Kim and Goldie 2008). When there are relatively few characteristics models based on group averages (“cohort models”) might be used. A greater number of characteristics may require several cohort models for different co-morbidity and age strata. As the number of characteristics (and the number of levels required for each) increases, models based on individuals are likely to become the more practical choice. Such Individual-level models (“micro-simulations”) can record individuals’ initial characteristics, how these change over time, and historical factors such as prior health states or interventions.

The target population can be modeled as open or closed. If the population is open new members can enter as time progresses; this approach could be used to represent an ongoing program of intervention, and is often used as a basis for model-based budgetary impact calculations. If the population is closed, members of the population enter only at the beginning of the model; this approach corresponds more closely to the clinical or medical sector perspective discussed earlier, and is often used in health technology assessments, for example, a 60-year-old with established disease. Models with open populations are more often used to model ongoing interventions, such as annual screening or vaccination. Closed population models are more often used to evaluate one time interventions in specific populations. Modeling a series of cohorts can bridge the two approaches. The USPSTF develops guidelines for clinical practice and the mammography evaluation modeled a closed cohort of women born in 1960, with screening starting no sooner than the year they turned 40.

2.4. Health outcomes modeled in the analysis, which may be measured as events, cases of disease, deaths, quality-adjusted life-years, disability-adjusted life-years, or other measures important to decision makers and stakeholders, should be directly relevant to the question being asked.

Health outcomes can be represented in many ways. Models may represent outcomes using clinically defined health states or events. Examples of these might be myocardial infarction, acute hepatitis B infection, or cancer death. The modeling objective might be to find the strategy that minimizes the rate of clinical events. Such clinically defined events may take the form of changes in, thresholds reached for physiologic parameters (e.g. glomerular filtration rate) or events or processes that are experienced by patients (e.g. cancer progression, or cancer death). Health outcomes may be subjective (e.g. anxiety associated with waiting for biopsy results) or objective (the results of a biopsy), or both. They may also be represented in the form of health indexes (e.g. quality-adjusted life years, disability-adjusted life years) that characterize health using a single vector composed of separate measures of quality and quantity of life, and occasionally, other factors (age or equity adjustments). Broader (aggregate) metrics of health outcome popular with funding agencies (as they facilitate budgetary allocations across different disease areas) include quality-adjusted life years and disability-adjusted life years (used mostly in low-middle income countries). In these cases health indexes are used to characterize the health
status of modeled individuals using a single vector composed of separate measures of quality of life and these are combined with survival (quantity of life) and occasionally other factors such as age or equity adjustments, to generate the aggregate metric. The USPSTF used deaths avoided (lives saved) and life-years gained to summarize the health outcomes of mammography screening.

Some models focus on outcomes that are events such as cases of disease prevented by vaccination or detected by screening, hospitalizations averted, and days of work absence averted. Such outcomes are usually important because they have been demonstrated to be associated with better health and longer life. These modeled ‘event’ outcomes may be referred to as ‘intermediate outcomes’, however this should not be confused with the use of ‘intermediate’ physiological variables (such as tumor response, blood pressure, glomerular filtration ratio..) that are may be used to project ‘final outcomes’ in a model by means of risk equations represented within that model. Other models (addressing issues of process efficiency in health care delivery) may not explicitly represent health outcomes at all, but only processes (waiting times, number of emergency department visits, and length of hospital stay) that may only indirectly linked to health status. Nevertheless it is generally recommended that “models should include long-term or final outcomes”.  

Some models may not explicitly represent health outcomes at all, but only processes (wait times, number of emergency department visits) that are only indirectly linked to health.

The ultimate goal of health care interventions is better health and longer life for the target population. Modeling the relevant outcomes, or events in the course of an intervention that are related to these final endpoints usually requires creating a series of intermediate disease states that track the progress of the disease and the effects of interventions on its course. A realistic model will include each aspect of the disease that may result in significantly different outcomes. In the mammography evaluation, these intermediate disease states were the stages at which breast cancer is detected clinically or through screening.

In addition to the beneficial effects, the adverse effects of interventions should be modeled to produce an accurate picture of their effect on health. If adverse effects are not automatically captured, as they are in the mortality rates associated with treatment, they need to be modeled separately. The USPSTF mammography evaluation included false-positive screens, unnecessary biopsies, and overdiagnosis as adverse effects of screening, but did not include morbidity from unnecessary (or necessary) biopsies or from treatment (see Box).

2.5. Interventions or strategies modeled in the analysis should be clearly defined in terms of frequency, component services (including services that may have preceded the intervention and that would affect its course), dose or intensity, duration, and any variations required for target subgroups.

When the modeling study is intended to inform a choice between alternative health care interventions, the job of the model is to estimate the effects of interventions on disease outcomes and costs. It is thus critically important to model all practical and feasible interventions and variations of those interventions.  

The range of interventions considered should be set wider rather than narrower when there is a choice. Nevertheless, the range of interventions under consideration is bounded by the decision problem. Although there are various ways to intervene against breast cancer, such as promoting...
308 more physical activity for all women and using drugs like tamoxifen that can prevent cancer in high-risk women, the USPSTF
309 evaluation addressed only screening and indeed only screening based on mammography. The choice of alternatives for
310 comparison has a major impact on the estimated effectiveness, and cost-effectiveness, of each intervention and the model-
311 based result (effectiveness and/or cost-effectiveness) is only meaningful in relation to the comparison interventions
312 considered

313 The form interventions take will differ across countries and often within countries, reflecting the practice patterns common
314 in the particular geographic area of for a particular population group. Thus what is labeled the same intervention ("breast
315 cancer screening") may be more or less effective, and more or less cost-effective, depending on the practice patterns
316 commonly in place in the geographic area where the target population lives. Practice patterns in the US are different from
317 those in Europe, and both are very different from practice patterns in low-income countries. The model should reflect the
318 practice patterns that apply to the target population, but it is important to specify the components of those patterns in
detail so that users of the analysis can determine how well the analysis reflects their situations.

319 The USPSTF mammography evaluation investigated 20 screening strategies defined by the frequency of mammograms, the
320 age at which screening started, and the age at which it ended. Screening confers benefit only if it leads to more effective
321 treatment than waiting for clinical diagnosis. The evaluation considered two patterns of treatment: ideal treatment (best
322 practice), and the treatment patterns actually observed in the US.

323 3. Although data are an essential component of a model, the conceptual structure of a model should be driven by the
decision problem or research question and not determined by data availability

324 Recommendations 2 and 2.1 describe the wide-ranging process of reading and consultation that should take place in the
325 early stages of developing a model. While data considerations will influence the discussion from the outset, they should
326 not drive the conceptualization of the model, which should consider all aspects of the disease, the target population, and
327 the interventions that may be important in driving model outcomes. It is rarely the case that no data are available. Expert
328 opinion and observational data (case reports, case series, and cohort studies) are nearly always available. What is often
329 missing is data of high quality, or data of high relevance (correspond exactly to the population in the model). Even when
330 data are not available for specific strategies, or specific features of the decision problem and model, it is usually possible to
331 explore their potential impact on outcomes through sensitivity analysis and value of information analysis. It is important
332 that the features of specific software packages should not be allowed to determine the structure of the model. The guiding
333 principle should always be that the model should represent the decision problem, not the best available data.

334 3.1. The choice of strategies/comparators crucially affects results, and should be determined by the decision
335 problem and not by data availability or quality. All feasible and practical strategies should be considered.
Constraining the range of strategies should be justified.

337 Comparisons should address all interventions that are relevant to the decision problem. These may be specific alternatives,
or a distribution of alternatives that reflects routine practice (also called ‘standard practice’), or even no intervention (the
339 ‘natural’ course of disease). When standard practice has been to “do nothing” (which rarely means literally doing nothing
but instead means not to screen or not to prescribe a drug), the intervention should be compared with this “do nothing”
alternative. If the intervention(s) of interest can be offered in different forms, for example screening at different intervals, or medicating at different dosages, these alternatives should be included and compared with each other. See above (recommendation 2.5) for more discussion of the range of interventions that should be modeled.

3.2. The time horizon of the model should be long enough to capture relevant differences in outcomes across strategies. A lifetime time horizon may be required.

Best modeling practice is to use a time horizon long enough to capture all important outcomes. This is often taken to be the remaining lifetime of patients, the time horizon used in the USPSTF mammography evaluation.

The choice between a closed and open model affects the choice of time horizon. A cohort simulation is implicitly constrained by the lifetime of the cohort. This is not the case for open models, where the modeler needs to make separate decisions about the duration of the program, and how long the model should be run to capture program effects.

Projecting over patients’ lifetimes usually requires extrapolating well beyond the available data, since trials and observational studies rarely cover such a long period. Thus short-term effects and costs may be based on directly measured primary data, while longer-term effects and costs must be extrapolated using various statistical models.

Previously, the Panel of Cost Effectiveness in Health and Medicine recommended analyzing several time horizons: “a short-term horizon that includes only primary data and a long-term horizon that also incorporates modeled data.”15 When future costs and health outcomes are discounted, as is recommended in cost-effectiveness analysis, the impact of using a lengthy time horizon will “be effectively limited by the discount rate.”

There may also be secular trends in the disease over patients’ lifetimes or changes in the nature of the disease. For example, when vaccination is successful against the serotypes covered by the vaccine, those serotypes not covered may over time become more widespread (‘serotype replacement’). Secular trends in disease may be observed. For example, the decline in use of hormone replacement therapy has been associated with a decline in breast cancer incidence. If these trends are likely to have a significant effect on the disease or intervention over time, and thus on the outcomes projected, they should be incorporated into the model, at least for purposes of sensitivity analysis. It is however generally not useful (or feasible) to project future trends in treatment for the disease of interest (or co-morbidities) beyond current practice including the introduction of the intervention of interest.

Valuing Outcomes. Models require a value structure, a way of valuing outcomes. Costs and quality adjusted life years (QALYs, or, in developing countries, disability adjusted life years, or DALYs) are the most common ways of expressing value. The literature on methods for costs and QALYs/DALYs is too vast to summarize here.14,18 ISPOR has developed a series of methodology papers related to the use of these outcome measures.22-29

Resources use and costs. Interventions use resources. It is important to describe the resources used by the modeled interventions in detail so that the nature of each intervention is clear and others can tell whether it reflects the way the intervention would be applied in their situations. Resource use is typically valued in monetary terms. Costs can be modeled for the short or the long term. In the short term certain resources, such as the numbers of hospital beds or trained mammography technicians, are fixed, and it can be prohibitively expensive or impossible to increase them. In the longer term these resources could be increased or decreased as necessary at much more reasonable cost. Most clinical
guidelines are intended for long-term use and thus the long-term approach, conventionally used in cost-effectiveness analyses, is appropriate for guidelines development.

As noted earlier, the medical sector perspective is used by the majority of studies that investigate costs. All budgetary costs incurred by the medical sector are included under this perspective. Costs that fall outside the medical sector, or that do not involve money payments, are excluded. If an analysis adopts the societal perspective, these costs should be counted as well.

Because the USPSTF bases its recommendations on effectiveness, but not on cost, the evaluation of mammography reported very little in the way of resource use: the number of mammograms required for each screening strategy; and the number of unnecessary biopsies. No money costs were reported.

QALYs/DALYs. Some models focus on intermediate outcomes such as cases of disease prevented by vaccination or detected by screening. Intermediate outcomes are important primarily because they lead to better health and longer life, so “it is generally recommended that models should include long-term or final outcomes”.14 Lives or life-years saved, unadjusted for health status, are the simplest measures of final outcomes. Increasingly, however, measures that incorporate quality as well as length of life are used: quality-adjusted life-years (QALYs) in high-income countries and disability-adjusted life-years (DALYs) in middle- and low-income countries.21 The USPSTF used deaths avoided (lives saved) and life-years gained to summarize the health outcomes of mammography screening.

4. The conceptual representation of the decision or problem should be used to identify key uncertainties in model structure where sensitivity analyses could inform the impact of structural choices. For example, where a lifetime horizon is used, the impact of alternative methods of extrapolating beyond the observed data should be explored.

Each of the decision made in the conceptualization of the problem concerning the population studied, the perspective, the time horizon, the interventions, the choice of comparators and the outcomes evaluated have the potential to alter the results of an analysis. During the conceptualization of the problem, experts and modelers can identify those key assumptions that should be evaluated through a structural sensitivity analysis. It is important to note that this may have an impact on choice of modeling type: some sensitivity analyses that require a change in structure of one modeling type may reduce to a parameter sensitivity analysis in another type.

5. The policy context of the model should be clearly stated. This includes who funded the model, who developed the model, whether the model was developed for a single application or multiple potential application, and who the policy audience for the modeling work is.

The development of health models is often explicitly linked to policy questions. Health technology assessment agencies often commission new models to evaluate the cost-effectiveness of drugs and technologies. Many countries require the submission of pharmacoeconomic evidence, in addition to clinical evidence, if a drug is to be listed on a national, state, or provincial drug benefit formulary. The policy relevance of this kind of model is high. The close linkage between model development and policy may have implications for model construction, as modelers will work within the context of specific methodological guidelines that reflect the views, priorities and values of decision makers30,31 (Guidance for Manufacturers and Sponsors Guidance for Manufacturers and Sponsors). The policy context of the model should be clearly stated. This
includes who funded the model, who developed the model, whether the model was developed for a single application or multiple potential application, and who the policy audience for the modeling work is.6

Other models may be developed by academics or independent investigators without a specific policy application in mind. The objective may be scientific discovery, the evaluation of broadly relevant clinical strategies, or the development of a generic model platform that can be subsequently employed to address specific policy questions.32 The intent may be to influence practice or reimbursement decisions, but there is no obvious or single decision maker. The immediate policy relevance of this type of model may be low.

Models may facilitate the development as well as the implementation of policy. In this approach, a model serves as the architecture for organizing evidence related to a specific policy initiative, and helps to generate policy questions as well as answering questions. The Patient Outcome Research Team for the secondary and tertiary prevention of stroke (Stroke PORT) was an example of this type of initiative.33,34 The modeling team considered a wide range of interventions to guide current practice as well as future research. The model showed that improving anticoagulation practice among patients with chronic atrial fibrillation offered the greatest potential clinical gains. This led to a randomized trial of anticoagulation practice improvement in the managed care setting.35

Matchar developed a taxonomy of models according to their place in the policy development process. Facilitated models are those which are developed for a specific policy purpose (the first example). Free standing models are those developed without reference to a specific clinical policy (the second example above). Embedded models are those which are integrated within the policy development process (the third example).36

The policy context may also have an undesirable effect. Pharmaceutical and device manufacturers have strong financial incentives to gain access to specific markets. When model-based economic analyses are required for market access, there is a correspondingly large incentive to reach a favorable conclusion. The published evidence suggests that sponsorship bias is likely to exist, and may be substantial.37-39 Bell showed that cost-utility analyses funded by industry were approximately twice as likely to show favorable cost-effectiveness ratios, relative to those with non-industry funding.38 Whether these effects are mediated through selection effects (only products with substantial effectiveness are subject to economic evaluation,40 choice of comparators, choice of parameters, study interpretation, or publication bias is uncertain.

Sponsorship bias may also be present in analyses funded by health systems. Payers have large incentives to constrain costs. New technologies with the potential for widespread diffusion and high costs may be analyzed differently than technologies with a lower potential system impact.
Section 3. Conceptualizing the Model

Once the problem has been conceptualized, the modeler must choose a specific type of model. The appropriate description of the problem in terms of the audience, population, disease, scope, time horizon and intervention options considered will affect the appropriate structure and components of the problem that are to be included in the model. The appropriate type of model is determined by a series of factors, including purpose, level of detail, and complexity. To illustrate, consider the example of a coin toss. At its root, there is nothing random about a flip of a coin. If one sought to understand the physics of a coin toss or to portray the real-world behavior of the coin as faithfully as possible, one might well construct a descriptive model that took into account such considerations as gravity, angular momentum, air resistance, the force applied to the coin, and the height from which the coin was dropped. But if one’s aim were to advise the Captain of a football team on whether to call “Heads” or “Tails” before the kickoff of next week’s game, one might adopt a more normative view, urging him to ignore the physics, to reject “objective truth” as the purpose to be pursued, and to focus more directly on the choice at hand. A decision model that treats the outcome of the coin toss as a random event with a 50% likelihood of “Heads” and a 50% likelihood of “Tails” might prove more fit for purpose as a guide to action.

There are several modeling types that can be used: these models differ by whether they model individuals or cohorts, and whether they are deterministic or stochastic. There are several published reviews of these types of models, an extensive catalog of model types and their characteristics is beyond the scope of this paper. Rather, this paper will describe the attributes and characteristics of problems that lead one to favor one of the major modeling types described in the methodology papers in this series: state transition models, discrete event and agent-based models, and dynamic transmission models.  

6. An explicit process (expert consultations, influence diagrams, concept mapping, or similar method) should be used to convert the conceptualization of the problem into an appropriate model structure to ensure that the model reflects current theory of disease or the process being modeled.

Rationale: (Task force opinion)

The process of moving from a conceptualization of the problem to an appropriate model type and structure is an important step in model development. Decisions at this step often define the set of simplifications and assumptions that are used to create a representation of the problem, and provide a written, explicit record of the process by which the conceptualization is instantiated. It is therefore important to have content or subject area experts involved in this process. The documentation of this process forms the foundation of the ability of a model to maintain transparency. The task force realizes that the formality of this process may vary substantially with the scope of the problem being created, but believes that there are substantial benefits to having an explicit process. There are published reviews of specific methods such as influence diagrams, and concept mapping and a general exposition of the model creation process in simple models is also found in Detsky.

One advantage of adopting an explicit process at this stage is that it supports focused discussions with content experts such as clinicians and policy makers who may not be sophisticated modelers allows on what is included in and excluded from the model, in particular the (simplifying) assumptions that have been made to represent the decision problem and treatment/disease process.
There are often several types of models that are suitable for the decision problem, and versions of each of the three modeling types in the series can be used for the same decision problem. Some problems are more naturally represented in certain modeling types than in others.

Rationale: (Task force opinion)

Common structures for creating models include simple decision trees, state transition models, discrete event simulation, agent-based simulation, and dynamic infectious disease models. Each model type has specific advantages. Simple decision trees may be useful to represent straightforward decision problems that are based on short time horizons and where estimation of the outcomes is relatively straightforward. State transition models are useful for representing events whose rates vary over time or the effect of interventions that span long time frames (especially in chronic progressive disease). Individual microsimulation or discrete event simulation (DES) structures are useful for building substantial complexity into the representation of what happens to patients in a particular model. When resource constraints and interactions between individuals in the model are required, DES and agent-based models are designed to represent these components; similarly, dynamic transmission models are useful when interactions occurring between groups within the model have an important impact on the model results.

The following recommendations provide guidance for the types of characteristics that might lead one to use one modeling type over another. It is important to note that virtually any problem can in principle be represented in any type of model, and therefore these recommendations are not prescriptive. Rather, some modeling methods are simply designed for particular types of problems, and it may be easier to represent a particular problem in one type over another. For example, given enough branches and nodes, one could develop a decision tree model that would return the same answer as a much simpler state-transition model, but this model might be extremely large, complicated to construct and check for errors, and potentially very difficult to change. The purpose of this section is to provide guidance regarding the characteristics of a model that support the selection of a particular modeling method.

Characteristics that Affect Model Selection

Several characteristics of the problem need to be considered in order to decide which modeling method makes the most sense. The modeler needs to decide whether the model will represent individuals or groups, whether interactions between the individuals occur, which time horizon is appropriate and whether time should be represented as continuous or discrete and whether there are resource constraints to be considered.

Unit of representation: Individuals vs Groups

Patients can be represented in different modeling structures either as individuals or as members of a generally homogeneous cohort. For example standard decision trees, Markov processes, and infectious disease compartment models represent populations as cohorts that are homogeneous within each state or component of the model. Individual microsimulation, discrete event simulation, and agent based models represent each patient in the cohort individually, and calculate population-based (cohort) outcomes by summing the outcomes across individuals. Modeling at an individual level does not automatically imply greater degree of accuracy. Many state based or cohort models can be very detail regarding
the characteristics of the subgroups model and very specific regarding the impact of a decision or choice on those cohorts. However it is generally easier to represent the biology or physiology of a particular process in a modeling system that represents each individual. The choice of unit of representation is also important because it changes the way that individuals or groups in the model may interact with each other. Whether or not the individuals can be “regarded as independent” will impact on the most efficient modeling method. Another reason for choosing whether to represent patients as individuals or groups depends upon the importance of the level of granularity of the variables that are used to predict future outcomes. For example, consider a model in which the person’s creatinine (a measure of kidney function) is important in predicting the likelihood of a particular event. When modeled as a group (i.e. to define different health states), the representation of creatinine level for each group will need to be as a categorical variable, such as whether cohort members have renal failure or not (for example creatinine level \( \leq 2.0 \) mg/dl or > 2.0 mg/dl). For variables that are not used to define the group (health state) a representative value will need to be obtained for each group. Although there is theoretically no limit to the number of such groups that may be created, potentially valuable information may be lost by categorizing variables or obtaining representative values for specific groups. Models that represent individuals are not so constrained, and patient characteristics may be retained as continuous variables, from which specific values are elicited for each patient as required over time. Representing how these variables change over time may add some complexity, but if risks of important future events are highly sensitive to the value of a continuous variable, this would tend to suggest using a model that represents the cohort as individuals rather than as groups.

**Interactions between individuals and other components of the model**

A second characteristic is whether it is important to represent interactions between individuals in the model, or whether the problem relates directly to a specific individual or group of individuals. This needs to be addressed when considering infectious diseases, such as HIV/AIDS. For example, if the decision problem is concerned with evaluating the appropriate treatment strategy for a patient with HIV, it is not always necessary to include the effect of that treatment on the epidemic itself. Early applications of the Cost Effectiveness of Preventing AIDS Complications (CEPAC) model evaluated appropriate treatment initiation and prophylaxis regimens for nosocomial infection (among other aspects of patient management) for patients already infected with HIV. The results of such a model do not require an evaluation of the transmission of HIV between individuals. The results of such a model did not depend on an evaluation of the transmission of HIV between individuals. However, evaluation of strategies to mitigate the effects of HIV requires modeling these effects on the epidemic itself. When the problem requires modeling the effect of an intervention on the spread of the disease between individuals, modeling methods designed for patient interaction include dynamic transmission models, discrete event simulation and agent based models, which are also particularly adept at modeling special characteristics. Similarly, when individuals interact with other components of the model, such as use resource that are limited, and therefore form queues and bottlenecks, agent-based models, discrete event models and even dynamic transmission models are appropriate methods for representation.

**Time horizon and time measurement**
The time horizon of the model represents how far into the future the particular model attempts to represent outcomes from a decision. In general, the time horizon is dictated by the scope of the problem that is being represented in the model. For example, a model representing strategies for the treatment of acute dysuria in young women could appropriately have a very short time horizon as there are virtually no long-term sequellae of this problem. Conversely, a model representing the effects of cardiovascular risk factor intervention would likely require a time horizon that included the entire lifetimes of the patients in the model who were being represented. The choice of the time horizon should be explicitly stated in model development. It is important to mention that the time horizon considered important by the decision maker may not incorporate the entire time horizon of the specific disease or problem. When this is the case, the modeler should be explicit about the reasoning for the time horizon chosen. In general, models with very short time horizons may be appropriate for decision trees; longer time horizons typically require one of the more dynamic modeling methods (state transition, discrete event, agent based or dynamic transmission models).

Similarly, the modeler needs to assess whether time should be modeled continuously or in discrete cycles. State transition models require that only a single transition may occur within the span of a cycle: this can often require potentially very short cycle times if the likelihood of events is high.

The above described characteristics imply the following recommendations for choosing a particular modeling type:

### 7.1. For relatively simple models, or decision problems with special characteristics (e.g. very short time horizons, very few potential outcomes) a decision tree may be appropriate.

**Rationale:** (Task force opinion)

Although decision trees are becoming less common in the literature, there are several advantages to their use. They are typically simple to conceptualize, create and modify, and can be useful tools to rapidly outline the components of a particular problem. They are most useful when the set of potential outcomes is relatively small and defined, when the time horizon of the problem and interventions is short, or when the future consequences of a decision made now is known with some certainty. Two classic examples of the use of decision trees are in the treatment of acute dysuria in women and the use of thrombolytics in the elderly. A primer on the use and creation of decision trees is available.

### 7.2. If the conceptualization involves representing the disease or treatment process as a series of health states, state-transition models are often appropriate as they may be simple to develop, debug, communicate, analyze and readily accommodate the evaluation of parameter uncertainty. Their primary disadvantage, the Markovian assumption that transition probabilities do not depend on past history, can be addressed by increasing the number of states. Individual-based state-transition models (termed microsimulations), which do not require this assumption, are an alternative when the number of states grows too large.

**Rationale:** (Task force opinion)

State transition models are ubiquitous in the modeling literature, and make the most sense when the problem or disease has been conceptualized as a series of homogenous states that define the relevant components or characteristics of the problem. State transition models are often consistent with a categorical clinical view, where the disease is broken into distinct stages or characteristics, such as the definition of cancer stages, the presence or absence of a disease state.
Conceptualizing a model

7.3. When the disease or treatment process includes interactions between individuals, the modeling methods should be able to represent and evaluate the effects of those interactions (dynamic transmission models, discrete event simulation models, agent-based models)

Rationale: (Task force opinion)

The defining capability of transmission models, discrete event simulation and agent-based models are their innate ability to represent interactions between individuals in a model or interactions of the individual with other characteristics or structure in the model. Therefore, when the conceptualization of the problem involves the effects of interactions of people or patients within the model (transmission of disease from infected to uninfected, allocation of specific organs to specific individuals on a waiting list) one of these modeling techniques is the most appropriate choice. Furthermore, these models all represent time continuously, rather than in discrete time cycles, and therefore may more easily or accurately represent or instantiate continuous risk functions, incorporate time-to-event data,

There are characteristics which also differentiate among these three modeling types. Dynamic transition models, which require the definition of states or “compartments” that represent the classification of people in the model (such as susceptible, infectious, or immune patients), may become analytically complex when the characterization of the problem becomes detailed, and are prone to a similar type of state-expansion that sometimes plagues cohort-evaluated state transition models. When a model that needs to represent interactions is large and clinically complex, discrete event or agent-based models may be a more appropriate modeling tool. Similarly, if the conceptualization represents geography or spatial proximity, it is much easier to represent those attributes in a discrete event or agent-based model.

7.4. When the problem involves resource constraints, the modeling method should be able to represent and evaluate the effects of those constraints (DES, Agent-based)

Rationale: (Task force opinion)

Similar to the problem of interactions between individuals in the model, some conceptualizations of problems requires that individuals interact with other parts of the problem. For example, questions regarding scarce resource allocation such as organ allocation policies for transplantation, distribution of antiretroviral medications in resource-poor environments, the appropriate scheduling of operating room cases to minimize surgeon wait time, or the number and location of distribution sites required for vaccination or treatment distribution during a pandemic, all required the modeling system to be able to represent competition for resources, the development of waiting lists or queues. Discrete event simulation and, more recently, agent-based simulation, were essentially designed for these types of problems and were first developed for representing production process and manufacturing processes in operations research and industrial engineering.
7.5. **For some decision problems, combinations of model types, hybrid models, and other modeling methodologies are appropriate**

Rationale: (Task force opinion)

The set of models described in this series of papers is not intended to be exhaustive. These methods represent the more common modeling methods currently used in the evaluation of health care problems. However, not all problems are most easily represented in these common platforms. There has been recent interest in developing models of physiology, and the creation of in silico simulations of disease, which do not fit precisely into these standard modeling types, that have been used to model sepsis, inflammation and the effect of therapies. The complexity of disease and treatment has also required the use of techniques from several modeling types. The Archimedes model is an example of such a hybrid, utilizing multiple differential equations that represent physiology operating inside an agent-based model that represents individuals, their disease, and their interactions with treatments and the health care system.

8. **Model simplicity is desirable for transparency, ease of validation and description. However, the model should be sufficiently complex to answer the question at a level of detail consistent with the problem being modeled, and to preserve face validity to clinical experts. Greater complexity may be necessary in policy models that may be used for many decision problems.**

Rationale: (Task force opinion)

The use of the correct level of detail is one of the most difficult decisions a modeler faces. Models that are too simplistic may lose face validity because they do not incorporate aspects of the problems that content experts feel are absolutely required, but models that are too complex may be difficult to build, debug and analyze, and may be difficult to understand and communicate. Einstein is widely credited with noting the same conundrum in the development of theories of physics, with the statement: “everything should be made as simple as possible, but not simpler.” As discussed in section 2, the scope, perspective, target population, specific outcomes considered and the interventions in the evaluation all contribute to the level of detail that is required to appropriately model the particular problem.
Figure Legends

Figure 1. **Development and construction of a model.** The numbers in the figure represent the methods papers in this series: 1) the conceptualization paper, which describes the conceptualization of both the problem and the model; 2), 3) and 4) which describe the three main kinds of modeling methods addressed, including state transition model, discrete event and agent based models and dynamic transmission models; 5) parameter estimation used to calibrate the models, and 6) the transparency and validation of a model.
**BOX 1. Defining the objectives, scope, and policy context of a model (here, 6 models):**

**Effects of mammography screening under different screening schedules.**

<table>
<thead>
<tr>
<th>Decision problem/ decision objective</th>
<th>To evaluate US breast cancer screening strategies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy context</td>
<td>This analysis was used to inform the 2009 US Preventive Services Task Force recommendations on breast cancer screening.</td>
</tr>
<tr>
<td>Funding source</td>
<td>AHRQ, NCI</td>
</tr>
<tr>
<td>Disease</td>
<td>Breast cancer: 4 models included ductal carcinoma in situ, 2 did not; cancer was characterized by estrogen receptor status, tumor size, and stage in all models and by calendar year in 3.</td>
</tr>
<tr>
<td>Perspective</td>
<td>Stated as societal. Health outcomes are breast cancer outcomes for patients. Limited modeling of resources used (see below). The US Preventive Services Task Force does not consider costs in making its recommendations.</td>
</tr>
<tr>
<td>Target population</td>
<td>Cohort of US women born in 1960. Subgroups were defined by age and the disease characteristics noted above. Subgroups mentioned in the report but not analyzed: BRCA1 and BRCA2; black; comorbidities; HRT; obese.</td>
</tr>
<tr>
<td>Health outcomes</td>
<td>Reduction in breast cancer deaths and life-years gained; false-positive results; overdiagnosis. Explicitly not included: morbidity from unnecessary biopsies or from treatment.</td>
</tr>
<tr>
<td>Strategies/Comparators</td>
<td>Screening: 20 mammography screening strategies defined by frequency (annual or biennial), starting age (40, 45, 50, 55, or 60), and stopping age (69, 74, 79, or 84); no screening. Assumed 100% compliance. Followup treatment: ideal and observed patterns.</td>
</tr>
<tr>
<td>Resources/costs</td>
<td>Number of mammograms, unnecessary biopsies</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Remaining lifetime of women</td>
</tr>
</tbody>
</table>
Figure 1.

Conceptualizing a model

Reality: health care decision, process and disease

Conceptualizing the Problem

Conceptualizing the Model

1) Decision/Problem
2) Disease

Data Sources

Modeling Type

Model Output

Model Users/Stakeholders

6
References


2. ISPOR. State transition models. 2011.


5. ISPOR. Calibration and Uncertainty paper. 2011.


Appendix: Examples of problem and model conceptualization: the case of HIV disease

We will use a series of examples in HIV disease to illustrate the components of good modeling practices. First, a broad conceptualization of HIV disease will be described, using an influence diagram approach, which might be the result of a process to conceptualize the problem being evaluated. Then, various types of questions will be posed that suggest a particular modeling method, and a paper using that technique will be described, including how the particular question being asked suggests the type of model used. This is not intended to be a comprehensive review of the use of modeling in HIV disease. Rather, it is designed to describe how various components of the conceptualization of the problem lead to preferences of one modeling type over another. As noted in the body of the paper, although many modeling methods can be used to evaluate the same set of questions, some problem formulations are more suited to specific methodologies.

Developing a conceptual model of the components of HIV disease

HIV infection is a complicated disease that has biological, physiological sociological and health system level components that affect the disease. HIV disease has been the subject of a large number of models from highly mechanistic models of virologic dynamics to various treatment decisions to public health strategies to control the epidemic. Figure A1 describes one of many possible conceptual model of HIV disease that could be developed in the course of modeling a particular problem. This characterization is not meant to be complete: rather it is designed to be illustrative regarding the process of matching a conceptual model of a particular problem formulation. Briefly, uninfected people may become infected with an acute HIV after which for a period of time patients are asymptomatic. They then develop symptomatic HIV infection and eventually may progress to develop AIDS with potential for nosocomial infections. Either as a result of screening or through presentation with symptoms, patients may be found to have HIV disease. After diagnosis, a series of treatments may or may not be initiated. Treatments provide substantial benefit, and change the biological picture of the disease by changing viral load and CD4 count, but also sometimes produce complications. Eventually all patients will die, whether or not they are on treatment. The disease can be characterized by multiple parameters in this particular illustration the disease is characterized by viral load and CD4 count. Viral load is primarily affected by whether the patient is on an antiviral regimen and whether the particular virus has developed a resistance to that series of medications. At a more biologic level, resistance develops through the combination of viral replication and mutation in the presence of selection pressure from a particular ARV regimen. Viral replication and ARV effectiveness is partially determined by adherence. Patient characteristics such as demographics, comorbid disease, social economic status, and many factors may affect a series of other components of the model, including causes of death, treatment complications, the likelihood of transmission and the decision to start an antiretroviral therapy. The disease can be known or unknown, the presence of the disease in a person or group can be determined through the use of the HIV test. The capacity of the health system may affect the ability to screen diagnosis and treat all those individuals whom would benefit by treatment. Future potential therapies, such as a potential HIV vaccine, could change the likelihood of progression from not HIV infected to Acute HIV infection.

Model using a basic decision trees
The complexity of HIV disease has made the use of simple decision trees uncommon in the evaluation of diagnostic or treatment strategies. However, there are several examples of simple decision trees used early in the evaluation of the epidemic. Johanson evaluated three different diagnosis and management strategies for the treatment of acute diarrhea in patients with AIDS. The authors could use a standard decision tree as the outcomes evaluated were relatively short-term (a short time horizon), and the long-term effects (survival) were assumed to be unchanged by the treatment of the diarrheal illness. The consequences of the decision (successful or failed diagnosis and treatment) occur within that short time frame, and the results of the decision affected only these short term outcomes. With these assumptions, the decision problem examines a very small component of our conceptual model of HIV disease, which would be a characteristic of problems appropriate for a simple branch and node decision tree. (Figure A2)

Model using a cohort based state transition model (see paper on state transition modeling for details)

As treatment for HIV disease improved in the early 1990’s, the impact of improved treatment on the benefits to screening various populations was unknown. Sanders et al developed a Markov model to investigate the costs outcomes and cost-effectiveness of various screening strategies in the presence of highly active antiretroviral therapy. Examining our conceptual model of HIV disease we can modify the figure to eliminate the components not directly applicable to this particular problem. Because screening programs are designed to find people who are asymptptomatically infected, this model ignores the development of HIV infection in patients who are currently HIV-negative, and also ignores evaluation of treatment of the acute infection (Figure A3). Similarly although the model they developed incorporates multiple cycles of therapy, the success of therapy, and the development of resistance, is modeled probabilistically in the component of the model that represents the treatment of HIV disease. The main components of the model involved case finding, and therefore the representation of the treatment phase of HIV disease is relatively straightforward and is characterized by average rates of virological suppression by cycle of therapy. The specifics of each regimen, i.e. the particular medications chosen, are not explicitly modeled. Similarly specific treatments for nosocomial infections are not explicitly modeled.

Because each of the components of the disease is treated somewhat categorically, (for example the states of disease and treatment are only characterized by levels of CD4 count, viral load, and treatment regimen) the model can be constructed as a Markov process, and evaluated as a cohort simulation.

The model has a partial consideration of the impact of HIV disease and treatment of HIV disease on transmission. Although it is not designed specifically to examine the impact of screening on the epidemic, it does allow for infected individuals to transmit their disease to uninfected individuals at rates proportional to their age their viral load and several other factors. It is necessary to do this to understand the impact of screening and treatment on the number of individuals that each patient may in fact which increase the cost and burden of the disease.

Models using an individual microsimulation state transition model (see paper on state transition modeling for details)
One of the most detailed examples of a microsimulation model of HIV disease is the Cost-Effectiveness of the Prevention of AIDS Complications (CEPAC) model. The model was originally designed to understand the cost-effectiveness various strategies to treat and prevent the complications of AIDS, and was expanded to evaluate value of triple therapy in chronic HIV disease. The model concentrates on understanding the impact of treatment on disease progression as represented by CD4 count and viral load, taking into account other patient characteristics and the development and treatment of HIV related complications. This particular use of the CEPAC model is not concerned with the development of HIV disease from patients who are currently not infected, nor is it concerned with acute or asymptomatic HIV-infected as all patients are known to be infected and are under consideration for therapy. Similarly, the early versions of the model represented the development of resistance probabilistically rather than as a direct relationship between viral replication and mutation, therefore detailed modeling of the development of antiviral resistance acquisition is not necessary.

The concentration of the model on the relationships between CD4 count viral load and the progression of HIV disease provide insights as to why modeling this particular problem as a Monte Carlo microsimulation is also appropriate. The complexity involved in the combination of regimens, resistance patterns, patient characteristics, viral load and CD4 count would require literally thousands of states if constructed as a standard cohort simulation state transition model, which is indicated by the multiple copies of the states at CD4 Count, Viral Load, and Patient Characteristics in figure A3. The use of microsimulation, in which one entity passes through the model at a time, allows for a significant amount of detail to be incorporated into a series of equations that govern transitions rather than in the definition of various states. The model has complete information about how long each patient has had HIV disease, what regimens they have been on, what infections they have had, and what the history of their CD4 count and viral load has been. It is this complexity that strongly suggests that the model be constructed as a microsimulation, rather than a cohort-evaluated state transition model.

Similarly, the model reported by Braithwaite considers many of the components already considered in the CEPAC model but in addition concentrates on the development of anti-retroviral resistance in the HIV virus, and directly models viral replication mutation and patient adherence to ART regimens (Figure A4). However similar to many cohort or microsimulation models, it does not incorporate any direct representation of infected individuals spreading the disease to uninfected individuals. As with the CPAP model, because so many components of the disease are considered the number of states required for a standard Markov process would be prohibitive and therefore this model was also constructed as an individual Monte Carlo microsimulation.

**Model using discrete event simulation (See DES modeling paper for Details)**

One of the most compelling characteristics of a problem that favors the use of a DES model is the requirement of modeling interactions between individuals (the spread of infection from one individual to another or the interaction of the individuals with potentially constrained resources (a limited supply of antiretroviral doses). One of the early representations of HIV disease as a DES model is presented in Leslie, which described the difficulty of representing significant clinical detail in a dynamic transmission model. A more recent example of a standard application for DES modeling is the evaluation of different allocation strategies to treating HIV disease in the presence of resource constraints. This model was designed
specifically for the purpose of predicting the clinical impact of providing limited doses of HIV therapy to patients on a first-
come first serve basis compared with a strategy that allocated doses to those with lower CD4 counts. The model includes a
disease progression component based on CD4 count that is mitigated by the presence or absence of treatment. Figure A6
illustrates the basic components that this model takes into account; notable, it now includes health system capacity and
the limitation that places on treatment. There is no representation of the impact of these two strategies on the spread of
the epidemic, nor is there significant detail regarding the development of resistance, nosocomial infections, etc. The paper
finds lower morbidity and mortality in a cohort treated according to CD4 count limits as opposed to first-some first-serve.
This illustrates how models that allow for interaction or resource constraints can be useful and instructive even in the
absence of significant clinical detail. DES models are not the only method that can incorporate constraints: resource
limitations can be incorporated into dynamic transmission models as well (by limiting the flows between states). Zaric et al
evaluated the impact of expanding methadone maintenance programs (which decrease HIV infection from heroin use and
other risky behaviors) on the clinical and economic costs of the HIV epidemic.11

Model using a compartment model (See dynamic transmission model paper for details)

Compartment models have been used for many years to understand the impact of mitigation strategies on epidemics. In
HIV disease, they have been used to evaluate the heterosexual spread of HIV,12 the effectiveness of substance abuse
treatment programs to decrease HIV infection,13 even incorporating resource constraints.11 For this example, we describe
the evaluate by Long of the potential effect of and HIV vaccine on the spread of the epidemic. Figure A7 describes the basic
components included in their model. The compartments of their dynamic transmission model included many patient
characteristics (age, type of sexual partner), a disease progression module that included asymptomatic infection,
symptomatic infection and AIDS, progression through these states is related to CD4 count and the presence or absence of
treatment. The presence of treatment in an infected individual and the presence of having had the vaccine in an uninfected
individual mitigate the likelihood of transmission. Dynamic transmission models were designed to represent the
conversion of uninfected to infected individuals, and incorporate variables and characteristics that impact those transitions.

Summary

We have described a series of models related to problems and decisions in HIV disease for which specific modeling methods
were chosen. Characteristics that determined the most appropriate modeling methods include the time horizon that is to
be modeled, whether patients in the model are to be represented as individuals or groups, and whether the model must
account for interactions between individuals in the model or whether the individuals in the model may be subject to
constraints. These characteristics are not absolute: long time horizons may be accounted for in simple decision trees
provided the effect of current decisions on future events can be represented by single global outcomes, such=s as the effect
of the decisions on life expectancy., even though most modelers would choose a state-based transition model or a DES type
model for long time horizons as they may explicitly represent the longitudinal nature of natural histories and long-term
risks. Decisions regarding whether to use cohort-based simulation or individual microsimulation is somewhat more user-
dependent. As the state space expands to hundreds or thousands of potential states, it may be technically easier to
represent the problem as an individual microsimulation, although there is little (if any) theoretical difference between the
two. However, it the conceptualization of the problem requires that a particular variable or characteristic be included in the
representation as a continuous parameter, a modeling method that allows for each individual to be represented (state
transition model simulated as an individual microsimulation, discrete event simulation or agent-based simulation) may be
required.

When the problem requires the modeling of interactions between individuals, the modeling methods that incorporate this
explicitly (dynamic transition models, DES and agent-based models) are the more appropriate techniques. The decision
between using dynamic transition models vs a simulation technique (DES or agent-based) is somewhat less straightforward.
Our experience is that the representation of high levels of clinical complexity is much more difficult to incorporate into
dynamic transition models than simulation, whereas dynamic transition models may have the ability to directly provide
analytic answers and insights into the importance of particular relationships (often termed “structural properties”) that may
be less obvious to uncover in simulation models.
Figure Legends

Figure A1: Potential conceptual model of the relationships in HIV disease. See text for details.

Figure A2: Components of the HIV conceptual model incorporated into the decision tree model of Johanson, which evaluated treatment strategies of a nosocomial diarrheal illness in patients whom already had AIDS. Infection and the epidemic, disease progression, primary HIV treatment was not considered. Outcomes beyond the treatment of the acute illness were assumed to be equivalent across decisions.

Figure A3: Components of the HIV conceptual model incorporated into the state transition model of Sanders, which examined the cost effectiveness of screening for HIV disease. Patients were described in multiple categories of clinical characteristic, CD4 count and viral load, and there was and various screening strategies were applied to a cohort of patients with a mix of infected and uninfected individuals, but the transition between uninfected and infected was simply measured as a probability, avoiding the need for a dynamic transmission model. The model eventually contained several hundred states, which approached a limit of tractability. (personal communication, Sanders)

Figure A4: Components of the HIV conceptual model incorporated into the early individual simulation model of Freedberg, which was designed to evaluate the effect of various treatments of AIDS complications, but was later modified to include primary treatment and screening. The model characterizes patients through across many characteristics, ARV treatments, the presence of resistance, and continuous viral load and CD4 counts. The number of states required to represent all these characteristics is nearly infinite, and an individual microsimulation method was used.

Figure A5: Components of the HIV conceptual model incorporated into the individual simulation model of Braithwaite, which is similar to Sanders and Freedberg in terms of characteristics and CD4 counts and viral load, and also added a biologically-based representation of the development of antiretroviral resistance. This allows for remarkably realistic representation of the development of resistance, and allows for the development of a very wide array of resistance patterns, easily represented in individual microsimulation format.

Figure A6: Components of the HIV conceptual model incorporated into the discrete event simulation model of Linus, which examined allocation strategies for limited doses of antiretroviral therapy. Because the model represented reasonable complexity in the natural progression of CD4 count and HIV disease, and required the ability to impose resource constraints, a DES model was used.

Figure A7: Components of the HIV conceptual model incorporated into the dynamic transition model of Long, which used a dynamic transmission model to represent the potential for a hypothetical vaccine to mitigate the transmission of HIV. The effect of the vaccine is represented by changing the rates at which uninfected persons mixing with infected persons acquire infections. The model represented 144 compartments, with differential equations representing flows between these compartments.
References


Figure A1 – conceptual model

Figure A2 – Johanson
Figure A7-Long