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ABSTRACT
In evaluating new oncology medicines, two common modelling approaches are state transition (e.g., Markov and semi-Markov) and partitioned survival (PS) models. PS models have become more prominent in oncology health technology assessment processes in recent years. Our experience in conducting and evaluating models for economic evaluation has highlighted many important and practical pitfalls. As there is little guidance available on best practices for those who wish to conduct them, we provide guidance in the form of "Key steps for busy analysts", who may have very little time and require highly favorable results.

Our guidance highlights the continued need for rigorous conduct and transparent reporting of economic evaluations regardless of modeling approach taken, and the importance of modeling that better reflects reality which includes better approaches to considering plausibility, estimating relative treatment effects, dealing with post progression effects, and appropriate characterization of the uncertainty from modeling itself.
Three Learning Points

- There is an increasing use of partitioned survival (PS modelling) for the economic evaluation of oncology drugs, without widely available practical guidance for conducting these types of models. Understanding what not to do is intended to raise awareness and improve analyses that are submitted to HTA bodies.

- Structural assumptions made about extrapolation, relative treatment effects and what happens post-progression will often have a significant impact on estimates of cost-effectiveness. Analysts need to be clear about these assumptions and provide a means to analyze alternative assumptions for HTA bodies and the decision-makers they support.

- While there are both benefits and limitations to the different modelling approaches, the simplicity of PS modelling in particular may lend itself to oversimplifying structural assumptions. Given the widespread use of modelling in oncology HTA, we hope more analysts will employ good practices and that the demand for good practices will increase.

TEXT

Introduction
The use of health technology assessment (HTA) as a policy tool to support healthcare decisions, particularly for new medicines, continues to grow in prominence. At the same time, there has been an increased reliance on economic evaluation based on modelling[1], as clinical evidence is developed primarily to support regulatory decisions of whether a technology is safe and efficacious rather than addressing payer concerns of whether it is truly a good use of resources.[2]

Although standards for the conduct of health economic evaluation have not changed considerably in recent years[3], there has been increasing attention to modelling approaches, including tools for critical appraisal and best practices.[4] There has also been an evolution in the types of decisions and policies economic evaluation can support, including optimal care pathways, reimbursement decisions, and pricing agreements as well as recognition of the limitations of economic evaluation as a means to control expenditure growth in highly politicized contexts.[5]

Internationally, as well as in Canada, medicines for oncology have grown in both political and financial importance.[6] Demand for early access to oncology interventions and regulatory approval based on non-comparative or early clinical data without information about long-term impact on costs and health, have made this area particularly challenging for payers and the HTA
bodies that support them. It has also increased the necessity of modelling and extrapolation, as well as invited guidelines, debate and commentary about appropriate methods.[7–11]

In evaluating new oncology medicines, two common modelling approaches are state transition (e.g., Markov and semi-Markov) and partitioned survival (PS) models. The latter, also referred to as quality-adjusted survival analysis[12–14], is an area-under-the-curve modelling approach similar to Q-TWIST[15], in which average survival (and life-years) are calculated from overall survival curves.

PS models were developed as a method of estimating average time in ‘alive’ health states in individuals with progressive disease[12]. They were originally devised as a way of avoiding challenges with the effect of patient attrition on health-related quality of life measurement in these post-progression states.[12] A typical three-state PS model requires an overall survival (OS) curve as well as another curve to partition between ‘alive’ states, which in oncology is typically a state of pre-progressed disease. Average time in one or more “progressed but alive” (i.e., post-progression survival) states can then be calculated by subtracting the area between the curves with discounting if appropriate.

The incentive to use PS models is likely driven from HTA demands to evaluate the consequences of decisions to use new medicines that go beyond the timeframes of clinical trials potentially coupled with lack of direct comparative information and available patient-level data. Requiring fewer assumptions and data than state transition models, they may in some sense align with guidance that emphasize model simplicity.[4] Membership in partitioned states in PS models can be directly informed from extrapolated survival curves without the need for deriving individual transition probabilities between states. Like traditional state transition models, both costs and health state preference values (i.e., utilities) can then be assigned for the purpose of economic evaluation.

Many funding recommendations about new medicines in Canada and abroad have been based on PS models. A review of the 30 most-recent NICE cancer drug appraisals (from May 2013 to Feb 2016) revealed PS modelling informed 73% (22/30) of them.[11,16] Model structure issues, particularly those frequently associated with PS models such as extrapolation and assumptions of benefit post-progression, have also been shown to correlate with negative recommendations from the pan-Canadian oncology review (pCODR).[17] In the past several years, PS models have been used in the majority of new oncology drug submissions to pCODR.
Despite the widespread use of modelling for oncology in HTA, there is little guidance available on current best practices, particularly for those who wish to use PS models. This note seeks to fill this gap, and shares thoughts on how to conduct and report economic evaluations with an emphasis on the emerging practice of PS modelling, based on our collective experience in conducting, evaluating and interpreting them.

With tongue firmly in cheek, we provide our recommendations in the form of “Key steps for busy analysts”, who may have incentives to achieve favorable results and have very little time (and data) to produce them.

**Step 1 – Avoid current standards for conduct and reporting of economic evaluations**

Current international best practices for the conduct and reporting of economic evaluation emphasize the need to conceptualize models, and explain and justify approaches.[4,18,19] In many cases, the most appropriate approach is not clear—however, in principle, cancer can always be conceptualized in at least three health states—progression free, survival post-progression, and dead (Figure 1). Although uncertainty about what occurs post-progression may be more readily explored with state transition modelling approaches, PS models are very convenient because they align with trial endpoints as presented in most publications, and can be derived from summary information and survival curves for treatments that are usually presented. Their use of observed survival curve data may also make them seemingly easier to interpret for decision-makers. If one feels pressure to explain why a PS modelling approach was necessary, some popular explanations are that the choice to use a PS model was based on 1) its popularity, 2) precedence in terms of use in previous analyses, or 3) convenience given available data.[20] Be careful when using these justifications! Good practice suggests decision problems rather than data availability should drive the modelling approach taken.[4]

Decision-makers may want a model that goes beyond these simple health states and additionally considers discontinuation rates, adverse events, downstream treatment, treatment switching, drug wastage, appropriate comparators and other patient-relevant considerations. Accounting for these potentially important factors will require more effort and more data regardless of the modelling approach taken. PS modelling effectively precludes explicit consideration of the influence on progression or survival of successive lines of treatment relevant to your healthcare setting, especially if the trial ended early or these treatments were not (yet) used by patients in the trial.[21] To avoid extra work, one could 1) tell local decision-makers that the care pathways used in the trial are not generalizable but an unrecognized standard of care OR 2) that these trial-based care pathways are generalizable and will perform similarly to whatever has been
implemented in their own jurisdictions. The additional steps required to conceptualize and incorporate all details relevant to the decision problem can be tiresome for the busy analyst with little time.

Avoiding or misreporting other important details of the evaluation can also curtail scrutiny. A good first step, for example, is to use the terms PS model, state transition model, semi-Markov[22], or Markov[23] model interchangeably to avoid criticism. One may also want to avoid reporting the value of resources or health (e.g., quality-adjusted life-years or life-years gained) that accrues in the pre- and post-progression states separately. This is particularly important when extrapolation methods are employed that result in substantial benefits accrued after progression of cancer, when therapy is halted, and without an underlying rationale to support it. (See Step 4)

Of course, there are also many methodological choices that will help to achieve favorable results that have little to do with modelling per se.[24] One will find the standard approaches to lowering incremental cost-effectiveness ratios (ICERs) still work here: 1) Carefully select health state preference values (i.e., utilities – use high ones for progression free and avoid a wide range of estimates); 2) Use inappropriate or less effective comparators when possible; 3) Calculate average cost-effectiveness ratios rather than incremental ones (try also not to report the numerator or denominator of these ratios); 4) Use inappropriate or difficult-to-scrutinize costing methods and 5) avoid disaggregating resource use measures / costs wherever possible.

**Step 2 – Maximize survival benefits through extrapolation!**

A three-state model (progression free, progressed disease, dead) first requires time-to-event data for progression and death. For PS models, these can be derived from progression-free survival (PFS) and OS endpoints using aggregate (i.e., survival curves) or individual patient data for either treatment or comparator (or both, see Figure 1). Extrapolation from trial data generally requires a semi- or, more commonly, fully-parametric method for generating survival analysis curves.[10] Survival analysis curves may be generated from trial data of a new intervention itself, or using evidence from another study, disease registry, or meta-analysis.[8,10] State transition models require additional data to reliably determine probabilities between states, including transition to death post-progression.

Existing guidance intended to make the selection of a statistical extrapolation method transparent and consistent between analyses requires analysts to present an “assessment of the fit of all available parametric models, details on the statistical fit of alternative models, tests of proportional hazards, consideration of the expected pattern in the hazard over time, and a comparison to external or registry data.”[8] -- a lot of work! The first and obvious approach to
producing better results is to handpick parametric approaches and not systematically apply recommended selection criteria, based on a combination of visual inspection, statistical tests, and appropriate justification with respect to internal and external validity. A flowchart that summarizes a useful way to apply these criteria has been published that the busy analyst may also need to ignore.[8] If the steps in the flowchart need to be addressed, you may want to consider selecting curves that are statistically appropriate, but ignore clinical plausibility. This is a common approach. For example, of 32 NICE technology assessments that used a parametric model-based extrapolation technique, only one used external data as a means of testing the plausibility of extrapolation.[25] Luckily establishing external validity involves some judgment and conventional approaches are not yet established.[10]

A “quick and dirty” approach to extrapolation that may work is to show a few carefully selected curves and use the ones that appear to fit best to the existing trial data through “visual inspection” or a subset of tests alone. The shorter the observed data relative to the time horizon over which you wish to extrapolate, the more opportunity you have to fit curves that align well with observed data but still display a range of long-term projections. Once plausible alternative models are discarded outright, it should then be easier to justify not including these in the economic model or conducting the sensitivity of results to these choices.

The advantage of PS models based on single parametric forms is that it is more difficult to test the sensitivity of the results to assumptions about extrapolation since transitions are not explicitly modelled.[11] This may also create the appearance of less uncertainty! Although much more useful to decision-makers, try not to create a model that allows users to test the sensitivity of results to varying parametric forms. You may also want to stick to single parametric forms that assume observed events from the trial predict future ones in a straightforward fashion rather than more flexible approaches (e.g., piecewise using multiple forms, spline-based, or mixture cure models) that may be more clinically plausible. Be warned that model users unable to change extrapolation parameters may use alternate (and less accurate) approaches to sensitivity analyses such as reducing the time horizon as a means to modifying extrapolated survival benefits that are seen as unrealistic or are associated with uncertainty. Be aware, negative funding recommendations have been associated with concerns about uncertainty due to inappropriate extrapolation over large time horizons.[17]

**Step 3 – Be creative when estimating relative treatment effects**
Economic evaluation requires knowing the effect of treatment on progression and survival. This can be estimated from a trial with a relevant comparator directly. In many cases, locally relevant comparators have not been used in clinical trials, or the analyst will only have data from a single-arm study without a comparator. Don’t panic! Comparative treatment effects can be estimated
without direct evidence using a variety of exploratory statistical approaches. However, when models are based on survival analysis curves, a fun and easy approach is to overlay the PFS and OS curves derived from a study of your new therapy of interest directly on top of curves from other studies to create an unadjusted but compelling indirect comparison. Survival is a hard outcome, and (fingers crossed), those examining your analysis will focus on the intervention as the sole explanation for outcomes rather than adjusting for the influence of differences in study populations (e.g., gender, age, performance status, etc.), care pathways, trial procedures, or other analytic choices.

If unadjusted comparisons are not an option, you may need to consider newer approaches to indirect treatment comparison, such as matching-adjusted indirect comparison or propensity-score match-adjusted comparisons as a means to creating comparisons.[26] Indirect treatment comparisons are easiest to incorporate into a model when studies used to generate relative treatment effects are handpicked (rather than based on a systematic review)! Making the statistical code or original data sets unavailable to reviewers can prevent immediate scrutiny. Try again to steer away from current conduct and reporting guidelines for indirect treatment comparisons.[27,28] Their singular focus on justifying methods, accounting for important confounders and not breaking randomization will increase your workload!

Another awkward situation is that OS results from clinical trials may not reach clinically or statistically meaningful endpoints. As most people are willing to believe this is a result of the trial design rather than the drug, it also means the analyst must adjust for the impact of trial design factors such as crossover using individual patient data and justify assumptions required for these methods.[29] A quicker (and dirtier) solution can be found in estimating OS from a different source of information entirely. While this may not be easy to justify (just say “individual patient data weren’t available”), there could most certainly be plenty of other trials or registries to choose from.

Another fast solution is to simply apply a hazard ratio derived from a PFS curve and apply this to the OS curve. This assumes any time spent delaying progression will translate directly into survival benefits! Any application of constant hazard ratios also relies on the typically unrealistic assumption of constant proportional hazards over time, and independence of outcomes. Luckily, analysts infrequently test and report on these assumptions[30], and ignoring them can translate into significantly more QALYs than could be calculated directly from trial data.

Differences in survival can be further exaggerated in PS models when OS and PFS curves for the treatment and comparator groups are extrapolated independently (e.g., using different parametric
forms that imply different assumptions about the hazard function). State transition models using fitted approaches or modelling state transitions from individual patient data (i.e., multi-state modelling)[31] is more time consuming but can achieve the same result.[31,32] Be aware modelling survival independently may actually be fully justified in some cases, such as when the effect on PFS does not directly translate into a survival benefit or when the treatments being compared have different mechanisms of action, but the appropriateness of such assumptions are hard to assess either way. A quicker approach is to fit a parametric curve to one trial arm then apply a hazard ratio (without checking the proportional hazard assumption) from the trial to predict comparative effectiveness.[33] Tip: you may find more favorable ICERs from applying a hazard ratio to a comparator curve, rather than the other way around. Play around with this! Ultimately, you will find approaches that lower your ICER. The key is to downplay the sensitivity of the results to these many different structural assumptions.

Step 4 – Make simplifying assumptions about what happens post-progression

Even if you do all the hard work of estimating relative treatment effects using an approach that passes scrutiny, and this increases your ICER past your comfort zone, no worries, there is still a final opportunity to get the ICER where you want! A simplifying assumption often made in either a PS or state-transition model is that the treatment effect persists for the duration of the time horizon. Do not consider any changes in relative benefits over time, particularly any waning of treatment effect; you will have to ignore guidance[34] about this assumption as well. This can be characterized by hazard ratios that are constant (i.e., continued benefits) for the entire time horizon of a model, or with independently fit parametric survival functions that consistently assume lower hazards for the treatment arm than the comparator. For PS models, this works very well because they assume the risk of death in each treatment group is a function of time, whereas in reality, risk of death is usually a function of both time and health state. It also works particularly well when OS curves are already extrapolated optimistically.

While it is possible that a failure to account for the impact time in a progressed state has on mortality risk will not significantly impact results, be mindful this is a gross simplification and could be questioned. Moreover, a new therapy can directly increase the risk of dying after progression by making downstream treatments less effective. The new therapy can also appear to indirectly increase the risk of dying after progression through a selection bias, by reducing progression in healthier people at a lower risk of death.[35] It is also possible for new therapies to reduce the risk of dying post-progression. The good news for the analyst requiring less work is that there are often not enough data to check assumptions about the impact of progression – so the analyst may assume the same risk continues unabated and that hazards are not dependent on the progression event nor the time spent in a progressed state.
It is worth mentioning that the lack of individual patient-level data for creating reliable transition probabilities is your strongest ally. Luckily for analysts, manufacturers are not compelled to share these data and HTA bodies may not demand them. Without these data, models are limited to estimates based on extrapolations of the aggregate clinical trial endpoint data. The availability of IPD provides more flexibility, allowing direct estimation of treatment effects and adjustment for treatment switching in PS models, and for estimation of additional transitions such as that from progression to death, ideally by estimating all transition probabilities simultaneously using a multi-state approach. However, you may find that these approaches can change ICERs dramatically.[36] You may also need to deal with biases that arise from incomplete OS data.[35] Unfortunately, increased data sharing and availability may become a reality in the future[37], which could make it more difficult to make excuses and keep ICERs in the sweet spot! Remember, in oncology modelling, the less we know the better!

When PFS and OS curves are extrapolated independently within PS models, you may also run into a tricky situation where there are a higher percentage of people in the progression-free state than are actually alive. A bit hard to explain! Rather than changing your extrapolation parameters, you may simply want to downward adjust PFS benefits at the tail to account for this. If scrutinized, additional, more nuanced, methods have been developed to potentially deal with this issue[38,39]. They are less conventional, but may actually more accurately reflect the natural history of disease. A ‘piecewise’ approach which changes hazards at certain time points, may be more practical,[39] but again will require a bit more work.

An illustrative example of some of the many approaches to handing uncertainty in steps 2-4 is shown below (Figure 2). The figure shows that once the trial ends, the analyst can produce a wide range of differences in extra effects (ΔE) depending on whether considering only the observed data, assuming the relative benefit (OS HR) continues unabated indefinitely, or exploring piece-wise changing hazards that represents diminishing benefits over time. In this simple hypothetical example, these scenarios produce 5-fold differences in estimates of extra effect including a nearly two-fold difference between scenarios of relative benefits continuing or diminishing over time.

**Step 5- Assume no structural uncertainty**

The final step for the analyst interested in quick-and-favorable results is to assume the model provided represents an uncontestable and definitive analysis for the decision maker. The good news is that neither PS or state-transition models have been shown to always produce more favorable results and that there is still little empirical work illustrating differences in these
approaches.[36,40–42] Also encouraging is that unlike modelling in other fields, such as weather forecasting[43] and climate change[44], one modelling approach in healthcare, even for multimillion-dollar decisions, is often seen as acceptable! History trumps reason. Although sensitivity analyses can be conducted using plausible ranges of the larger number of assumptions that go into modelling, they will require a lot of time and effort. [45] Some hardworking analysts have even conducted both state transition and PS modelling approaches as a means to check the impact of structural assumptions; however, this is still the exception to the rule! [36,40–42,46]

CONCLUDING REMARKS
We hope this tongue-in-cheek advice will be useful for the hurried analyst. Luckily, there are no one-size-fits-all approaches in the area of oncology modelling, and a lot of room to manoeuver. As future empirical research emerges and methods become more established, we hope new avenues for creativity will emerge.

(MORE SERIOUS) CONCLUDING REMARKS
Despite some concerns raised about the use of oncology models in HTA, there seems to be no concrete evidence that any one approach systematically produces better or worse results than other approaches. It is possible that the more straightforward approach in PS modelling lends itself more to the various shortcuts and potential pitfalls highlighted here. We hope this guide reinforces the need for rigor in the conduct of oncology modelling, and the sensitivity of the results to the numerous choices made to conduct them. Given their prominence in HTA to support funding anticancer therapies, coupled with the large number of medicines being developed, and their potential additional costs, we hope more analysts will employ good practices and that the demand for good practices will increase. Understanding the impact of choices in analytic judgments, at the very least, requires transparent and consistent reporting of methods and results.

In addition to the need for rigorous conduct and transparent reporting of economic evaluations, we hope our ‘Key steps for busy analysts’ also highlight the importance of modelling that better reflects reality; this includes better approaches to considering plausibility, estimating relative treatment effects, dealing with post progression effects, and appropriate characterization of the uncertainty from modelling itself. They may also highlight the need for more time and better reporting for those who are fortunate enough to conduct and review these analyses. We would argue there is a need for elevated rigor and transparency of reporting regardless of what type of model is chosen. Perhaps the final frontier will be less focus on the final result, and more on how the result was achieved, and whether it really makes sense.


Figure 1. Three state conceptual model for cancer.
OS = Overall survival. Cancer can usually be conceptualized as a three state model with patients either alive or dead. Patients in an alive state have either yet to progress (i.e., have achieved an endpoint of progression-free survival) or have clinically significant disease (i.e., have achieved an endpoint of progressed disease, calculated by subtracting overall survival from progression free survival). Patients can die in either state, which is the inverse of their probability of being alive (1 – OS).
Figure 2. Illustration of effect on incremental cost-effectiveness of greatly differing assumptions related to benefits from extrapolation of overall survival in a PS model

When modelling based on trial data with a follow-up period that is short (6-12 months) relative to the time period relevant for decision-making (10-12 years), the relative effect of treatment ($\Delta E$) is greatly affected by structural assumptions related to how benefits continue beyond the period of the trial (extrapolation) and relative to standard therapy post-progression. Basing calculations on benefits observed in the trial could provide the smallest estimates, whereas assuming benefits seen in the trial continue for as long patients are alive will provide large ones. Structural assumptions made about extrapolation, what happens in each treatment arm post-progression and how relative treatment effects are ascertained (not shown here) often have a larger impact on estimates of effectiveness than any other factors. Being very clear about how these assumptions were made and making them amenable to change by decision-makers is important and may be ignored by the busy analyst.