Model Structure in Oncology: When Complexity Matters

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Every health economic model involves structural choices: how many disease states to include, how to represent post-progression disease, how to handle time-dependent transitions. These choices feel important, and they are. But they rarely receive the same scrutiny as data inputs.

We tested this directly in prototypical oncology models, comparing three- and four-health-state models alongside embedded and simplified approaches, all derived from the same underlying data. The answer, most of the time, is reassuring. But the exceptions are precisely where expertise matters.

The Question

In early-stage oncology models, disease progression can be represented with varying granularity. A simpler model might group all types of progressed disease (PD) into a single state. A more detailed model might distinguish locoregional recurrence (LR) from distant metastasis (DM), each with its own mortality risk, resource use, and trajectory. Similarly, models must decide how post-progression outcomes accumulate over time. Traditional approaches use "tunnel states" to track time spent in a state explicitly, whereas newer approaches achieve the same goal more efficiently.

The question is whether these choices meaningfully affect the bottom line for incremental life-years, QALYs, and costs, and if so, under what conditions.

Our Approach

Rather than compare models built from different data sources, confounding structural differences with data differences, we built multiple model structures from the same foundation. A lifetime discrete-event simulation served as a reference standard, generating patient-level data that parameterized each structure consistently.

Two comparisons were run in parallel:

- **State complexity[1]:** a three-health-state model (EF, PD, and Death) versus a four-health-state model, separating PD into LR and DM progressions
- **Within-state dynamics[2]:** three levels of complexity for handling post-progression outcomes, from a full embedded sub-model approach down to a simplified three-state structure

Results

In the base case, the structures agreed closely, well within any threshold that would matter for a reimbursement decision. The table below shows where results converged, and the specific scenarios where they diverged.

One finding stood out: more health states does not always imply a more accurate model. In scenarios where progression patterns shifted non-proportionally over time (e.g., an early wave of locoregional recurrence followed by a later surge of distant metastasis) the simpler three-state model actually tracked the simulation reference more closely than the four-state model.

	State complexity	Within-state dynamics
Base case	<1% difference in incremental LYs, QALYs, and costs between the models	<1% difference between the most complex approach; <6% vs. simplified 3-state model
When it matters	Non-proportional progression: when recurrence patterns shift substantially over time	Extended time in progressed disease states
Practical takeaway	The simpler model tracked the reference simulation more closely in complex scenarios implying more states isn't always better	Embedded approach preserves post-progression history accurately, without the overhead of explicit tunnel states

Why It Matters

These analyses were methodological in focus, but the practical implications are straightforward.

- **Structural choice should be driven by disease biology, not convention.** The right model structure depends on the natural history of the specific disease — particularly whether progression patterns are time-varying. Getting this wrong, in either direction, is a risk.
- **Structural validation should be routine, not optional.** Testing whether structural assumptions affect results is standard in parameter sensitivity analysis; it should be equally standard for model structure. Many models don't do this explicitly.
  Methodological rigor pays off at HTA. Reviewers are increasingly attuned to structural uncertainty. Being able to demonstrate that structural choices were deliberate and tested, not just inherited from a prior model, strengthens an HTA submission.

The Red Nucleus Difference

This is the kind of question our team builds into model development from the start, not as an afterthought, but as part of how we think about structural credibility. If you're planning a cost-effectiveness model for an oncology program and want to discuss how structural choices might affect your submission, we'd welcome the conversation.

References

1. B. White, S. Milev, et al. Comparing three- and four-health state... ISPOR (2026). *Forthcoming.*
2. B. White & S. Milev, Embedded-Markov models…, SMDM Annual Meeting (2024).