Patient-Level Simulation Modeling for Economic Evaluations: Opportunities and Challenges in a Practical Setting

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BACKGROUND

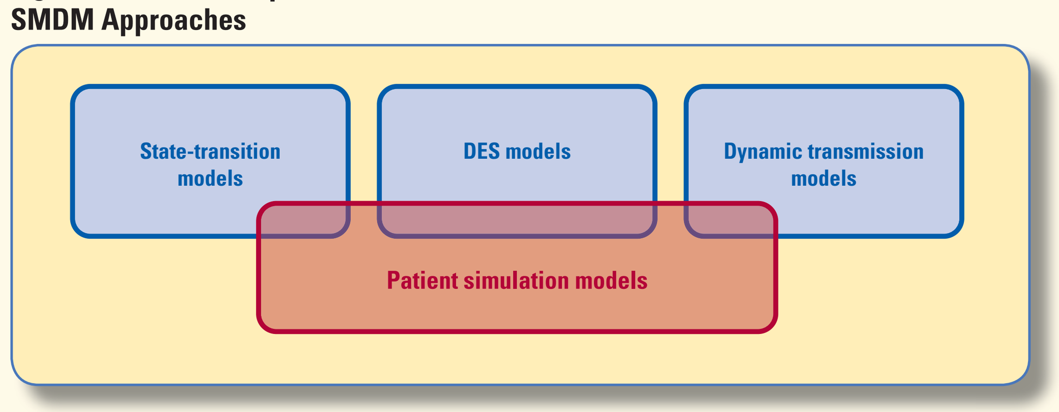
- The ISPOR-SMDM Modeling Good Research Practices Task Force reported on three broad categories of modeling techniques for conducting economic evaluations: (1) state-transition models, (2) discrete event simulation (DES) models, and (3) dynamic transmission models.[1]
- Choosing an appropriate modeling approach depends on the characteristics of the decision problem and requires balance between transparency, efficiency, and complexity; advanced data and software requirements also must be considered (Table 1).
- Patient-level simulation modeling can be approached from the state-transition perspective (as a Monte Carlo simulation), the DES perspective, or the dynamic transmission perspective (as an agent-based model) (Figure 1).
  - Regardless of the selected perspective, patient-level simulation is noteworthy for its flexibility in reproducing patient experiences that closely mirror reality.
  - This flexibility is especially important when modeling health conditions with continuous or multi-dimensional health states or with non-Markovian dependence on disease history.
  - The advantages of patient-level simulation modeling often come at the expense of advanced data and software requirements and reduced computational efficiency.
- When patient-level simulation modeling is used for economic evaluations, methods for exploiting the opportunities while mitigating the challenges are needed.

Table 1. Overview of ISPOR-SMDM Characterization of Three Common Modeling Techniques

Modeling Technique	Characteristics	Trade-offs
State-transition	• Health conditions (including relevant history) can be represented by a manageable number of states • Can include Markov cohort models and Monte Carlo patient-level simulations	• Transparent • Computationally efficient • Limited flexibility and complexity • Minimal software requirements
Discrete event simulation	• Patient pathways strongly influenced by health history • Consideration of limited or constrained resources • Interactions between individuals	• Increased complexity • Flexibility to match patient experiences to reality • Reduced transparency and efficiency • Advanced software requirements
Dynamic transmission	• Interventions against infectious diseases that impact disease transmission • Can be deterministic or probabilistic and population- or individual-based	• Increased complexity • Flexibility in modeling disease transmission dynamics • Reduced transparency and efficiency • Advanced software requirements

Source: Caro et al., 2012[1]

Figure 1. Relationship Between Patient-Level Simulation Models and ISPOR-SMDM Approaches



METHODS

- Based on our experience developing patient-level simulation models in Microsoft Excel for a complex, progressive disease, we identified steps that can be taken during the development and presentation of a spreadsheet-based simulation model to capitalize on the advantages inherent to this approach while mitigating some of the associated difficulties.
- Specific examples from our experiences are presented for the purpose of illustration.

RESULTS

Basic Principles

- We identified three basic principles that can be generalized to reduce computational complexity, improve transparency and efficiency, and improve face validity when developing spreadsheet-based patient-level simulation models for economic evaluations.

1. *Reduce computational complexity* by minimizing the model's dependence on random number draws wherever possible.
2. *Improve efficiency and transparency* by anticipating the random draws required to fully determine a patient's experiences and organizing the calculations so that a sufficient batch of random numbers can be generated before each patient enters the model.
3. *Improve face validity* by creating visual representations of sample patient experiences that highlight the ability of the model to capture the variability present in real-world settings.

Principles in Practice

- To demonstrate the first principle, consider a simulation model with a fixed time step where patients initiate treatment at the beginning of the modeling horizon and discontinue treatment at a rate of 10% per time step.
  - Treatment discontinuation can be modeled probabilistically by drawing a random number at each time step to determine whether the patient continues on treatment (Figure 2a).
  - In contrast, this same process can be modeled by tracking patients' cumulative probability of discontinuation over time and using a single random draw to identify the time step at which each patient's discontinuation occurs (Figure 2b).
  - By reducing the number of random draws required to simulate a probabilistic process such as treatment discontinuation, the complexity of the model's simulation engine can be greatly reduced.
- After reducing the number of random draws per patient, the second principle recommends organizing model programming so that the entire batch of random draws required for patient-level sampling can be performed at once (Figure 3).
  - Organizing the probabilistic components of the programming in this way allows the remainder of the calculations for a patient's experience to be deterministic, thus improving efficiency and transparency.
    - The gains in transparency are due to the ease with which users and reviewers will be able to identify the range of parameters subject to random sampling and to separate the sampling process from the disease progression- and outcome-focused calculations.

Figure 2. Example Using Cumulative Probabilities to Reduce the Number of Random Draws Required to Simulate Treatment Discontinuation

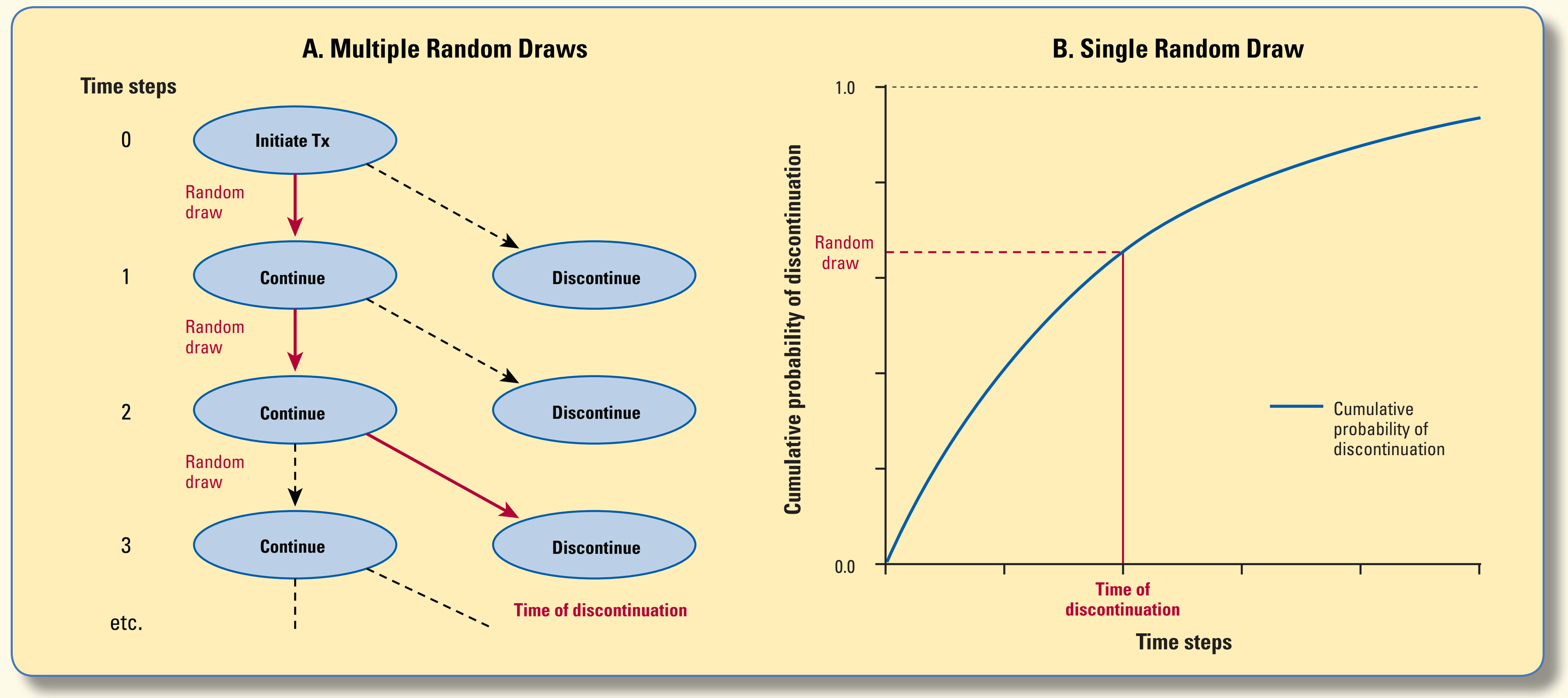
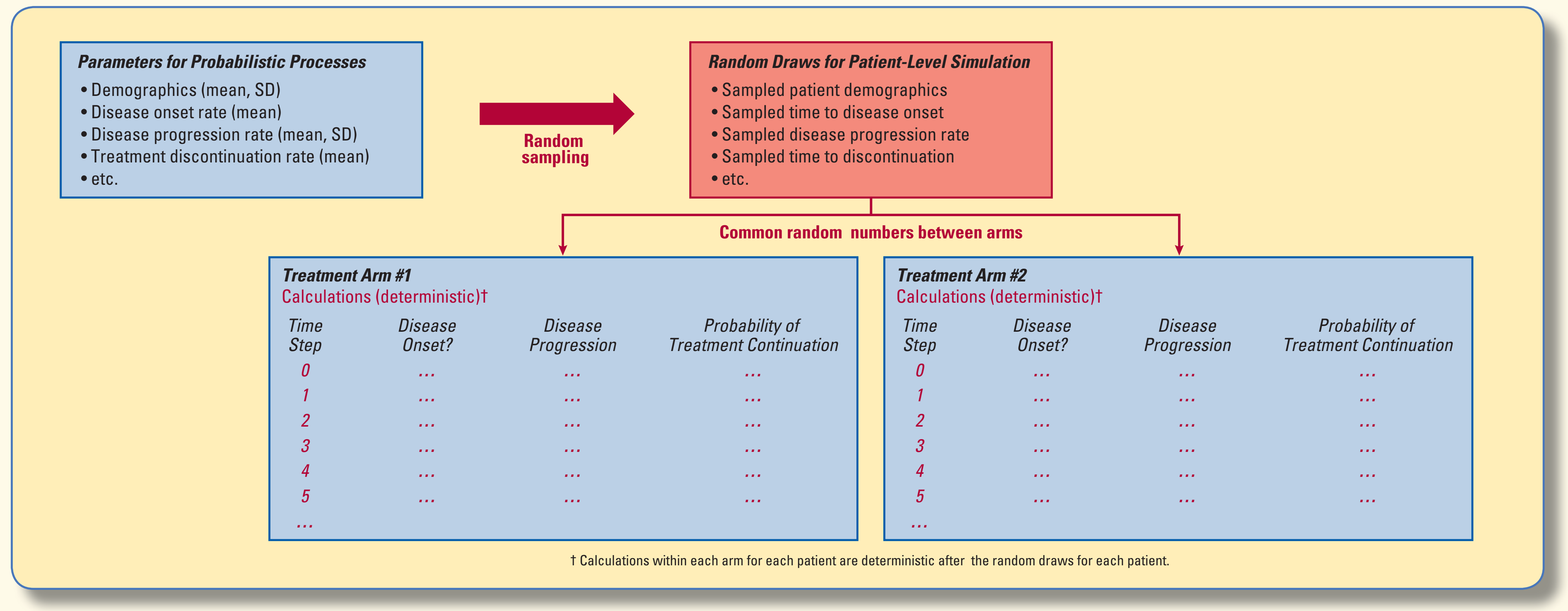
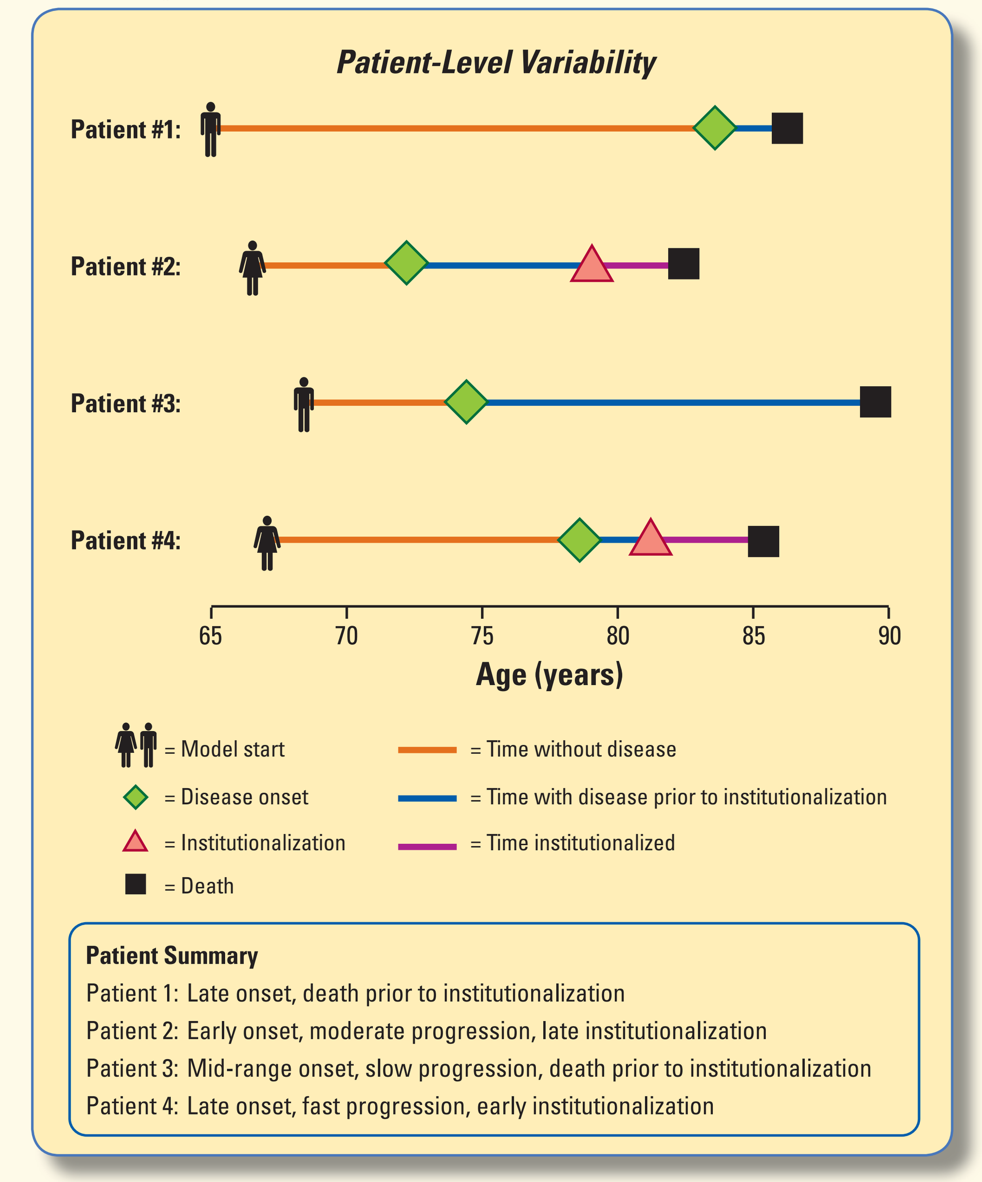


Figure 3. Organizing Random Number Draws and Model Programming to Improve Transparency and Efficiency and to Facilitate the Use of Common Random Numbers Between Arms of the Model



- Simulation models generating random draws on an as-needed basis require additional programming to manage the sampling process and the sequence of probabilistic events; avoiding this additional programming, especially in spreadsheet-based software, can greatly improve the efficiency of the modeling calculations.
  - This approach facilitates the use of common random numbers in the comparison arms of the model, an approach that ensures that the differences observed between the arms are due to treatment differences and not differences in the simulated patients.[2]
- The increased complexity, both in model structure and programming, associated with patient-level simulation can lead to barriers when communicating the modeling approach and results to decision makers.
  - In theory, patient-level simulation models enjoy a natural advantage in face validity over cohort models because they recreate patient experiences on a person-by-person basis, much the way a prospective clinical or epidemiological study would enroll and follow a variety of patients over time.
  - Our third principle looks to capitalize on this advantage by using simple visual representations of sample patient experiences (separate from a model structure or influence diagram) to communicate the modeling approach to nontechnical users.
  - While many specialized simulation software packages create visual sample paths automatically, programming a simulation model in less-specialized software such as Microsoft Excel requires researchers to create these tools on their own.
  - Figure 4 presents sample disease pathways for four patients diagnosed with a progressive disease from a disease-free state through the points of disease onset, institutionalization, and death; the graphic depicts how the model captures patient-level variability in the age at study entry, the age at disease onset, the point of institutionalization, and the age of death.

Figure 4. Sample Disease Onset, Progression, and Death for Four Patients With a Progressive Disease



CONCLUSIONS

- When patient-level simulation is used in the economic evaluation of new health technologies, researchers are faced with the challenge of capitalizing on the benefits of this approach while maintaining critical aspects of computational efficiency, transparency, and face validity.
- Our experience developing spreadsheet-based patient-level simulation models for a complex, progressive disease has demonstrated that the key principles described above can be applied successfully in a practical setting.

REFERENCES

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