Introduction to Disease Simulation: An Emerging Approach to Inform Decision Making

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Introduction

At the heart of quantifying the value of an intervention is the need to understand how its effects measured in a clinical trial will translate to benefits for patients over relevant time horizons (often their remaining lifetime) in a real-world setting. In rare cases, trials may be able to directly inform the required benefit, but in most cases it is necessary to use a mathematical framework — a model — to extrapolate beyond the trial-reported outcomes. This model, at its best, is a full *disease simulation*, detailed enough to handle the required predictions accurately and carefully validated to ensure its credibility. In this article, we provide an overview of disease simulation including its definition and applications, the types of data that can be integrated, and the communication of results. Our Archimedes Condition-Event (ACE) simulator of Alzheimer's disease (AD) will be used throughout to provide clarifying examples.

What is disease simulation?

A major purpose of a disease simulation is to inform healthcare decision making. It accomplishes this by integrating data on multiple components of a disease in a structure that is sufficiently detailed to address the decision makers' questions. These components include measures that describe the patients' condition, such as their demographic characteristics, treatment history, biomarkers, and patient-reported outcomes; and the resulting probabilities of experiencing events such as disease progression, hospitalization, or death.

A defining feature of disease simulations is that they predict the evolution of the disease components based on the clinical or physiological relationships between them. The focus on clinical and physiologically meaningful relationships affords a clear mechanism for evaluating how well a simulation may perform outside the range of the data used in its development. For example, describing the change in a trial endpoint directly from clinical trial data and extrapolating that change to longer times does not generally require a disease simulation; while the trial data must be extrapolated to longer times, alternate statistical fits are an appropriate way to test how that extrapolation influences the results.

In contrast, evaluating how a treatment might benefit a patient population that was not enrolled in the clinical trial would generally require a disease simulation. Such a question requires an explicit clinical hypothesis of the direct effect of the treatment, how that direct effect would interact with any differences between the trial population, and the population of interest and clinical evidence describing that interaction from outside the trial. A disease simulation is an effective mechanism for integrating this richer set of information and enabling alternate clinical hypotheses regarding the interactions to be tested.

Disease simulation is particularly useful for complex multifactorial conditions with many interacting markers. In AD, for example, understanding the impact of a treatment targeting early biomarkers of disease (e.g., anti-amyloid therapies) requires linking changes in those biomarkers to changes in cognitive, functional and behavioral measures, and those measures, in turn, to outcomes like institutionalization, quality of life, and costs. While there are a variety of data sources and published studies that connect various sets of these, a comprehensive understanding of the pathophysiology and progression of AD has yet to be developed. As such, an AD simulation makes explicit the clinical hypotheses linking the available data and permits evaluation of how specific decisions are influenced by alternate hypotheses.

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What types of questions does disease simulation address?

By connecting multiple components in a physiologically informed way and generating testable predictions, disease simulation is able to support decision making throughout the development process. One key application of disease simulation is estimating the implications of trial results for submissions to Health Technology Assessment (HTA) groups and payers. When clinical trials report only surrogate endpoints, disease simulation can predict how those will translate to clinical and economic outcomes of interest. At the same time, disease simulation can support forecasting of therapeutic benefit and market potential for different subpopulations. Explicit simulation of various patient populations allows for specific estimates of economic outcomes, such as cost-effectiveness and budget impact. These, in turn, can address the question of how expanding or restricting the indicated population for a treatment influences its cost-effectiveness and budget impact.

Before an intervention is ready for market, disease simulation can help evaluate risk and mitigation strategies in planned clinical trials. Outcomes that can be assessed through simulation of a clinical trial include the range of plausible outcomes, the risk of false positives or negatives, and the total duration and cost of a trial. Mitigation strategies that can be considered include changes to selection of population inclusion/exclusion criteria, endpoints, comparators, and duration of follow-up. Simulation of clinical trials under different clinical hypotheses regarding how components of disease are related also enables evaluation of risks associated with uncertainty regarding the true clinical pathology. It is important to emphasize that predicting the potential range of direct effects of a new therapy is, in general, outside the scope of disease simulation and best informed by clinical evidence.

Returning to the example of AD, many current clinical trial programs are evaluating the effects of potentially disease-modifying treatments in patients at the very early stages of disease. Given the incomplete understanding of AD pathophysiology, estimating the probability that a planned trial will yield positive outcomes under various clinical hypotheses provides valuable information that can help the trial designers make choices that minimize the risk of negative outcomes. Another critical question regarding early AD treatment is how its cost-effectiveness and budget impact will vary with the definition of the patient population. This is particularly so with intervention aimed at earlier stages of disease or even in pre-disease conditions. Disease simulation affords a mechanism to quantify both cost-effectiveness and budget impact, with explicit hypotheses regarding the disease process that can be effectively discussed with, and vetted by, clinical experts.

What types of information can be integrated using disease simulation?

While it is possible to generalize about inputs, it is essential to emphasize the information that should be used for an analysis with a disease simulation is driven by the questions specific to that analysis. Here we consider an analysis that requires simulation of the long-term clinical outcomes implied by short-term clinical trial data on a surrogate endpoint.

To address this question, the scope of the disease simulation must span both the clinical outcomes of interest and the surrogate endpoints. The simulation's scope must include the ability to predict the evolution of the clinical outcomes over long periods of time in a potentially diverse patient population. This scope means the following information should be considered in the simulation: the population being considered (characteristics and epidemiology); the relationships between the measures of disease and outcomes being modeled; the temporal evolution of at least some of those measures and outcomes; and how an intervention impacts the measures.

Direct clinical data, including that from clinical trials, registries, or other observational data sources, is the best source from which this information can be drawn, but there are often gaps in the available data or the clinical understanding of a disease. Clinical expert opinion can help bridge those gaps, but different possibilities should be tested in a disease simulation where feasible for a specific analysis. Additional data is required to bridge to patient outcomes such as institutionalization or healthcare resource utilization.

In our example of an AD disease simulation designed to support the evaluation of an early, disease-modifying intervention, the simulation's scope integrates data on early biomarkers of disease and their connection to cognitive, functional, and behavioral decline. While the biomarker directly impacted by the intervention being considered is key, the complexity of AD and the limited understanding of its true pathophysiology also need to be taken into consideration. Therefore, the appropriate scope includes additional related markers to allow more faithful representation of any clinical trial data and the testing of alternative hypotheses of the disease. In addition, the simulation uses information connecting the early biomarkers to cognitive function and ultimately to patient outcomes. To understand how the population treated influences outcomes, the simulation draws

from data about patient demographics, incidence, and prevalence, supporting consideration of budget impact and clinical trial enrollment.

How can disease simulation inform decision making?

The goal of a disease simulation is to inform decision making. To do so, it is necessary to ensure that the results are not just an appropriate synthesis of the available data, but clinically meaningful and broadly accessible. Disease simulation necessarily incorporates a substantial amount of information, particularly in complex disease areas. This can make it challenging for a decision maker to review a simulation directly or to interpret the results appropriately. It is, therefore, very important to present the design, underlying assumptions and clinical findings of a simulation, including its programming, in a comprehensive but transparent fashion.

One area for focus is the design choices and assumptions regarding how the included disease components are interconnected. These aspects may limit a decision maker's willingness to use the outputs of a simulation. In a well-constructed disease simulation, these assumptions can be tested by running different scenarios, allowing assessment of how the simulation results depend on them. This, in turn, fosters understanding of the credible range of outcomes and the likelihood of particular ones. Beyond this practice, however, the clinical hypotheses represented in the most important assumptions can be reviewed with clinical experts both in direct discussion and via publications.

Clear presentation of how the clinical features of the disease are translated into the simulation structure is important in enabling a disease simulation to be used with confidence. This includes both thorough documentation of the simulation design and accessible programming, which allows the equations to be easily viewed. The programming approach must be carefully considered from the earliest stages of simulation design to afford this clarity, while also enabling the flexibility to test multiple clinical hypotheses across a broad scope.

Finally, a well-designed disease simulation, given its clinically realistic extrapolations, is well-suited to ongoing predictive validation. Such studies can demonstrate the designed scope for a specific disease simulation and the types of questions it is suitable to address. It is essential, however, to emphasize that a significant fraction of the predictions from a disease simulation may ultimately not be borne out — the simulation is only as good as the underlying clinical hypotheses and will evolve over time. Predictive validation, however, provides a clear road map for continued advancement of the simulation and for systematic testing of a set of clinical hypotheses against new data.

Conclusion

Disease simulation is a powerful tool for understanding how an intervention may influence the progression and consequences of a complex disease. The types of questions best addressed by disease simulation, however, require modeling multiple components of a disease and a correspondingly substantial base of information. Appropriately designed disease simulations can provide a consistent framework to effectively inform decision making throughout the development process and subsequently.

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