Decision-making in cancer: Causal questions require causal answers

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Introduction

Treatment decisions in cancer care are guided by treatment effect estimates from randomized controlled trials (RCTs). RCTs estimate the *average* effect of one treatment versus another in a certain population. However, treatments may not be equally effective for every patient in a population. Knowing the effectiveness of treatments tailored to specific patient and tumor characteristics would enable individualized treatment decisions. Getting tailored treatment effects by averaging outcomes in different patient subgroups in RCTs requires an unfeasible number of patients to have sufficient statistical power in all relevant subgroups for all possible treatments. Instead, we must rely on statistical modeling, potentially using observational data from non-randomized studies to further the individualization of treatment decisions.

The American Joint Committee on Cancer (AJCC) recommends that researchers develop outcome prediction models (OPMs) in an effort to individualize treatment decisions [1, 2]. OPMs, sometimes called risk models or prognosis models, use patient and tumor characteristics to predict a patient outcome such as overall survival. The assumption is that the predictions are useful for treatment decisions using rules such as "prescribe chemotherapy only if the OPM predicts the patient has a high risk of recurrence". Many OPMs are published every year. Recognizing the importance of reliable predictions, the AJCC published a checklist for OPMs to ensure dependable OPM prediction accuracy in the patient population for which the OPM was designed [1]. However, accurate outcome predictions do not imply that these predictions yield good treatment decisions. In this perspective, we show that OPMs rely on a fixed treatment policy which implies that OPMs that were found to accurately predict outcomes in validation studies can still lead to patient harm when used to inform treatment decisions. We then give guidance on how to develop models that are useful for individualized treatment decisions and how to evaluate whether a model has value for decision-making.

Main

Predictions change the treatment policy. Individualizing treatment decisions means changing the *treatment policy*. For example, if for a specific cancer type and stage the current treatment policy is to give the same treatment to all patients, then individualizing treatment decisions means recommending treatments tailored to a patient's characteristics. The value of an OPM is not in how well it predicts under a certain historic treatment policy, but rather what is the effect of deploying this model on treatment decisions and patient outcomes?

Consider an OPM that uses baseline tumor characteristics to predict an outcome but ignores whatever treatment the patients may have had, i.e. *treatment-naive* models, such as Salazar et al. [3], Merli et al. [4], Courtiol et al. [5], Carmona-Bayonas et al. [6]. Interestingly, the decision to ignore treatments in the OPM is in line with the AJCC checklist for OPMs (item 12 [1]). However, these OPMs can cause more harm than good when used to support treatment decisions, even when they are accurate under the historic treatment policy. For example consider an OPM that predicts overall survival for stage IV lung cancer patients based on the baseline growth-rate of the tumor. An accurate model would predict shorter survival for patients with faster growing tumors. Applying this OPM, a clinician could decide to refrain from palliative radiotherapy in patients with faster growing tumors under the assumption that their life expectancy is too short to benefit from radiotherapy. This decision based on the OPM would be unjustified and harmful, as faster growing tumors are more susceptible to radiotherapy [7].

Prospective validation does not validate models for decision-making. The gold standard for evaluating the accuracy of an OPM is *prospective validation* [1, 8]. In a prospective validation, patient characteristics and outcomes are recorded for a new patient cohort according to a predefined protocol. Comparing the OPM's predictions with the observed outcomes provides an estimate of how accurate the OPM is outside the cohort in which the model was developed. The OPM from the lung cancer example above, if well-estimated, would be found accurate in a prospective validation that uses the historic treatment policy because the OPM was developed under the same historic policy. It would then fulfill all the AJCC checklist items but still lead to patient harm when used for treatment decisions because the differential effect of radiotherapy depending on tumor growth-rate is not accounted for in the OPM.

As an additional validation step, one may conduct a prospective validation study where the OPM is used for treatment decisions in new patients. If such a validation were carried out for the lung cancer survival OPM, the patients with fast-growing tumors would be given radiotherapy less often due to the predictions of the OPM, leading to even worse survival for these patients than before introduction of the OPM. The introduction of the OPM has thus caused harm, but paradoxically it is still found to be accurate in the validation study as the model already predicted that patients with fast-growing tumors have a poor prognosis.

Models should improve decisions. The crux of the issue with OPMs is that they answer the question "What is the chance of a good outcome, given that we know certain characteristics about this patient *with the assumption that we will keep making the same treatment decisions as we always did*?". Similar issues exist with other kinds of OPMs which make predictions using the historical treatments but without regards to the policy for how those treatments were assigned (i.e. *post-decision* models such as Ryu et al. [9], Fried et al. [10], Hippisley-Cox and Coupland [11], Liu et al. [12], Pires da Silva et al. [13]). Post-decision OPMs are also in line with the AJCC checklist (item 12 [1]). To improve treatment decisions however, we need models with a foreseeable positive effect on outcomes when used in decision-making.

OPMs assume treatment decisions follow the historical policy and thereby cannot estimate the effect of a new policy derived from the OPM. This reliance on the historical treatment policy leads to an insurmountable gap between OPM prediction accuracy and value for treatment decision-making in actual clinical practice. Figure 1 illustrates this difference.

Building models to individualize treatment decisions. One way to construct a good individualized treatment policy is with models of the interventional distributions. The interventional distribution for a patient with certain characteristics is the probability of the outcome under a hypothetical treatment and is equal to the probability of the outcome if a patient with those characteristics would be randomized to that treatment in a RCT [14]. The optimal treatment policy is one that selects the treatment that leads to the most beneficial expected outcome according to the interventional distribution.

Estimating interventional distributions requires unconfoundedness, which holds when there are no unknown variables that influence both the treatment policy and the outcome (i.e. confounders). RCTs are ideal for this as unconfoundedness holds by design because the treatment assignment is random. However, individual RCTs are generally too small to include many important patient and tumor characteristics in the modeling. Observational data from regular clinical practice on the other hand are often more readily available. If all variables that influence the observational treatment policy are available in a particular dataset, meaning that unconfoundedness holds, there are many approaches to estimating interventional distributions. These include 'conventional' statistical approaches such as regression or machine learning approaches, for example using neural networks [15].

An issue with estimating interventional distributions from observational data is that it is possible that confounders are overlooked or unavailable. In some settings where certain confounders are unavailable, the interventional distributions can still be estimated using specialized methods. Two examples are methods based on proxy-variables of unmeasured confounders [16, 17] and instrumental variable methods [18] and their machine learning variants [19, 20]. These methods rely on assumptions that may not hold perfectly in reality, so figuratively speaking they might reduce the gap between model accuracy and treatment policy value, but not close the gap entirely.

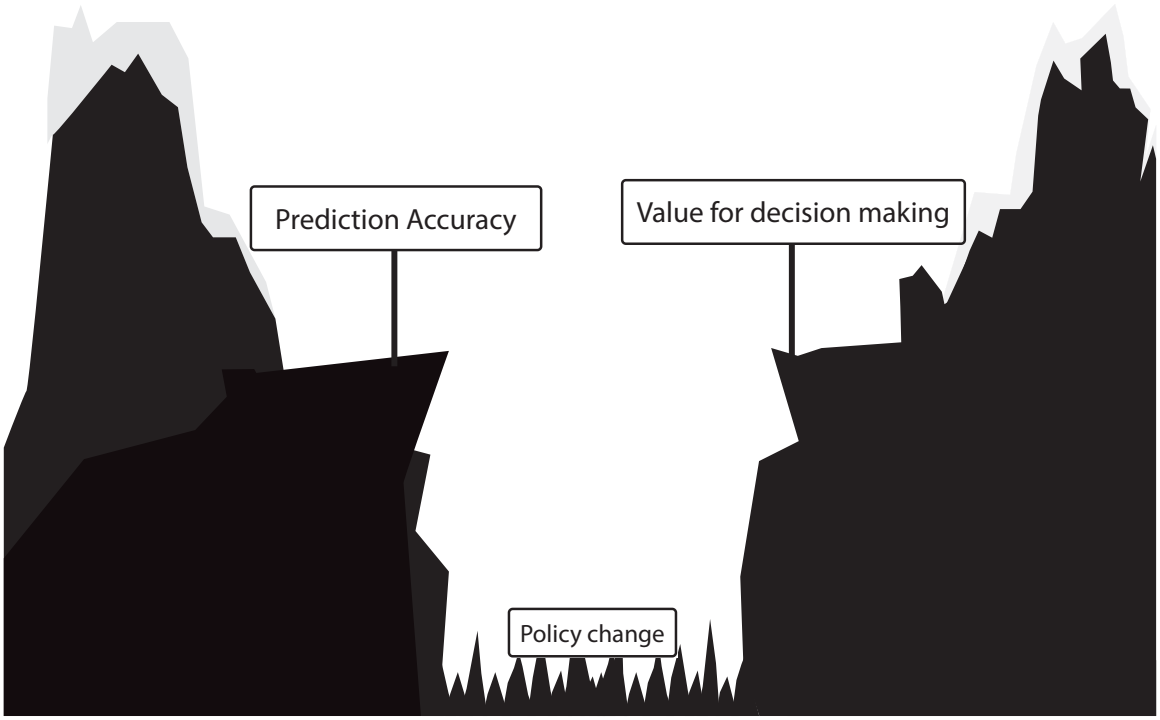

Figure 1: Illustration of the difference between outcome prediction model (OPM) accuracy and its value for treatment decision making. Validation of an OPM following the AJCC checklist leads to a reliable estimate of the OPM's accuracy. However, because the OPM relies on a fixed historic treatment policy, prediction accuracy does not imply value for decision making, as visualized with the gap.

A special interventional distribution is the untreated risk, which is the hypothetical outcome under no treatment (or some baseline treatment) and would be observed in the control group of an RCT. For instance, when deciding to give adjuvant therapy after breast cancer surgery, the untreated risk of recurrence is the risk of recurrence when no adjuvant therapy would be given. Knowing the untreated risk is valuable when considering to give no further treatment, and as a baseline to compare other potential treatments against. Although estimating the untreated risk requires unconfoundedness, in some cases it may be estimated quite accurately even from confounded data using offset models [21, 22].

How do we validate models used for treatment decisions? Because it is unknown beforehand how doctors and patients would act on new treatment recommendations, the ultimate test of the effect of introducing a new model for treatment decision-making is a *cluster randomized controlled trial* [8, 23]. In a cluster RCT some groups of clinicians are randomly selected to get access to the model while others are not. This allows for

the estimation of the effect of introducing the model on treatment decisions and patient outcomes. For example, the cluster RCT could demonstrate that using the model leads to fewer treatment side effects and better overall survival. However, in the context of shared decision-making, patients may weigh the value of overall survival versus treatment discomfort differently [24]. These individual preferences need to be taken into account in the cluster RCT when calculating the value of introducing a model for decision-making.

As an alternative to cluster RCTs, the expected outcomes under a new treatment policy can be evaluated in data from an RCT by calculating the average outcome in the subgroup of patients for whom the randomized treatment assignment was concordant with the recommendation of the proposed new treatment policy [25]. Such an analysis does not take into account that in practice the compliance with the new treatment policy might not be perfect. Because RCTs randomly collect data from different interventional distributions, models of the interventional distributions can be validated in RCTs with standard prediction validation approaches [8]. For shared decision-making, interventional distributions for different treatment options allow the patient to make their own judgment on how to weigh expected overall survival with expected treatment discomfort. As opposed to individual RCTs that randomize a patient to a certain treatment, cluster RCTs randomize clinicians' access to a model for decision support. Thereby individual treatment decisions may still be confounded in cluster RCTs meaning that cluster RCTs cannot validate interventional distributions directly.

Similar types of validation are also possible in observational data but require unconfoundedness and thereby sensitivity analyses for potentially omitted confounders [26]. Notably, prospective validation without model deployment as recommended in the AJCC checklist [1] provides no information on whether an OPM matches the interventional distribution which would make the OPM useful for shared decision-making, or what the effect is of deploying an OPM on treatment decisions and patient outcomes.

Discussion

In line with American Joint Committee on Cancer recommendations [1, 2] many OPMs are developed to individualize treatment decisions. The AJCC checklist provides important guidelines for OPM development and validation, such as clearly defining the patient population, predictor variables and prediction time-point, in addition to validation in external datasets. These items improve the dependability of OPMs for predicting outcomes in the intended patient population [1]. However, OPMs that satisfy all the criteria in the checklist still have unknown clinical utility because high prediction accuracy in prospective validation studies does not imply value for treatment decision-making in clinical practice. Because the gap between OPM accuracy and value for decision-making is due to causal issues, it is not resolved by larger datasets, more sophisticated prediction algorithms (e.g. machine learning) or even by prospective validation with model deployment. In contrast, we explained how models of the interventional distribution are useful for decision-making and how to validate any model used in decision-making.

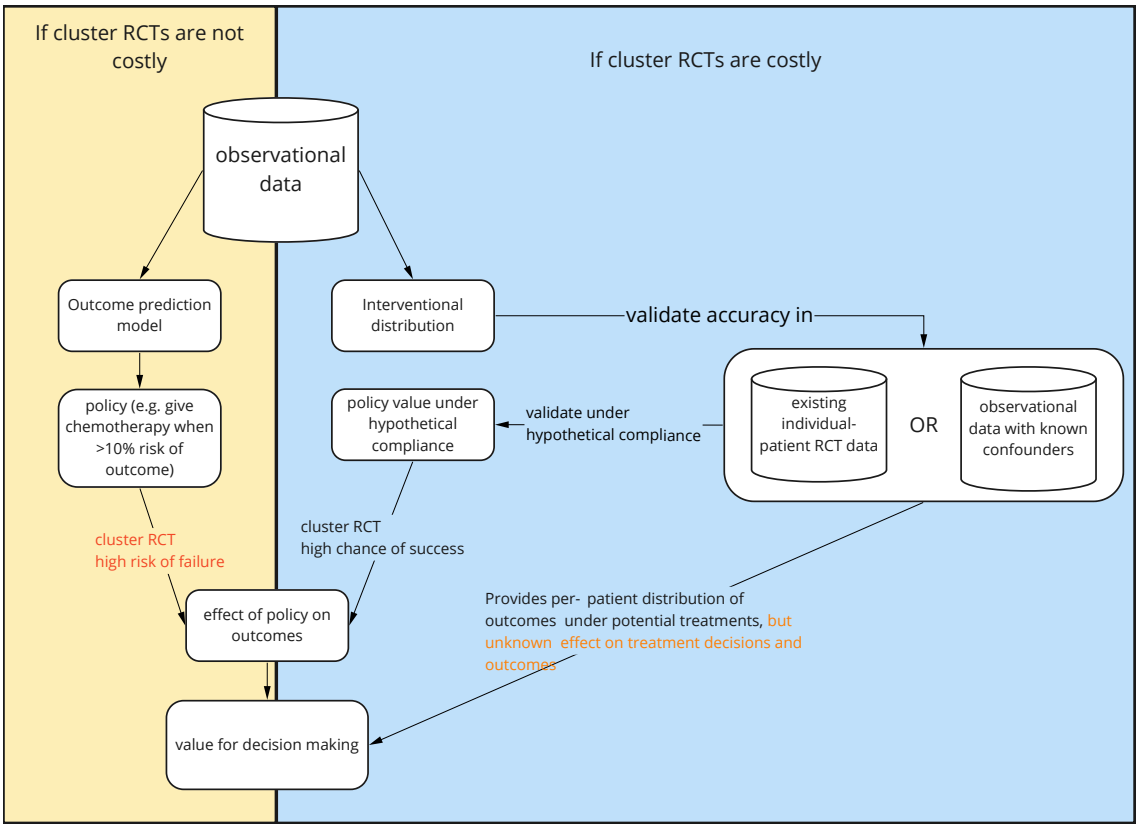

Figure 2: Flowchart of what to do depending on the costliness of cluster randomized controlled trials. Costliness of cluster RCTs should be taken broadly, including time, money and ethical considerations.

The gap between OPM accuracy and value for decision-making is due to causal issues, but it is different from the standard "correlation does not imply causation". In the standard "correlation is not causation" setting, all variables (treatment, outcome, patient/tumor characteristics) are already present in the historical data, whereas in this case, the output of the OPM cannot be a cause of the outcome. This is because the OPM is not a variable in historical data, but a shift in policy that changes the distribution of the treatment. It was noted before that cluster RCTs are the ultimate test for the impact of a new prediction model on clinical practice due to issues related to compliance [23]. We show that because of the gap between prediction accuracy and value for treatment decision-making for OPMs, many

accurate OPMs will fail to demonstrate value in cluster RCTs. Also, from the perspective of shared decision-making, prediction accuracy in standard RCTs may be a better test than a cluster RCT because of the difficulty of accounting for an individual patient's personal values and preferences in a cluster RCT.

Modeling interventional distributions is harder than developing OPMs due to the extra requirement of unconfoundedness, which involves gathering data on all confounders, more complex statistical estimation if some confounders are unavailable, and sensitivity analyses. When the cost to do a cluster RCT is low, it may suffice to build OPMs in line with the AJCC checklist and test them in cluster RCTs before model deployment. As illustrated in Figure 2, when cluster RCTs are costly, impractical or unethical, modeling the interventional distributions ensures models with foreseeable effects when used for treatment decision-making.

There is a classical distinction between treatment effect estimation and prediction that amounts to "treatment effect estimation is causal (and thus requires RCTs)" but "prediction is not causal". When it comes to individualizing treatment decisions with prediction models, this distinction is unhelpful and confusing. Selecting the best treatment for a patient is a causal question and requires causal answers.

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Patient involvement

Drs. Lidia Barberio, Director of "Longkanker Nederland" (the Dutch patient association for lung cancer) provided feedback on this perspective. Her input broadened the scope of this work making it more relevant for patients. Specifically, we added more emphasis on the importance of including the values of the patient in treatment decision-making.

Conflicts of Interest

We have the following interests to declare: no relevant competing interest for this article. PJ received consulting fees from Sanfit and Inozyme. TL is co-founder and shareholder of Quantib BV. The department of radiology at the University Medical Center Utrecht has a research collaboration with Philips Healthcare. WA was a PhD student at the University Medical Center Utrecht during most of the work for this perspective, but now works at Babylon Health Inc.