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The use and misuse of risk prediction tools for clinical decision-making

1. Introduction

Risk prediction tools are of great value in supporting clinical decision-making: they can identify, for example, the potential benefit of a treatment on prognosis of an individual patient, the risk of (late) health complaints, or the risk of further spread of a disease. These individual estimates can consequently be used to weigh the benefits of a certain treatment against its harms, which is crucial in the current era of personalised medicine. Additionally, more and more diseases are known to be very heterogeneous which is reflected in the necessity for prediction tools to incorporate the multifactorial influence of a wide range of different patient- and disease-related variables to provide accurate estimates.

A very well-known example of a clinical risk prediction tool in breast cancer is PREDICT [1], which has very recently been updated to a version including progesterone receptor expression [2]. PREDICT estimates individual overall survival probabilities for breast cancer patients, in combination with additional survival benefits of several adjuvant treatment modalities. The underlying model uses expected treatment effects obtained from randomised controlled trials and is specifically designed for treatment decision-making. A similar approach was used to develop the PORTRET tool – an alternative prediction tool specifically for older breast cancer patients – since the PREDICT tool was shown to inaccurately predict survival in this patient group [3].

1.1. Prediction tool development and use

Prediction tools which are intended to be used for treatment decision-making are different from prediction tools that are used to identify patients at risk in a screening context, or to personalise follow-up strategies after curative treatment for a certain disease. It is extremely important to distinguish these types of models from each other, as they have different purposes and are designed using different data sources and methodologies.

An example of a prediction tool that is intended to be used for a different purpose than treatment decision-making, is the INFLUENCE 2.0 tool [4]. It estimates individual time-dependent (conditional on the number of disease-free years) risks of locoregional recurrence, distant metastasis, and second primary contralateral breast cancer for patients who completed their curative treatment, including adjuvant therapies. The underlying model has been developed using data from the population-based Netherlands Cancer Registry and includes the variables age, tumour grade, tumour stage, nodal stage, multifocality, hormonal receptor status, HER2 status, type of surgery, and several adjuvant therapies. The estimates obtained by this tool are intended to be used to determine the optimal follow-up strategy for individual patients [4]. Patients with high risks in year one and two, but very low risks from the third year on could, for example, be more intensively followed-up in the first two years, but could perhaps get a much less intensive follow-up in the following years.

However, the estimates from INFLUENCE 2.0 must *not* be used to estimate the clinical effectiveness of different primary therapy options. In a recent scoping review of Zhao et al. [5], the authors incorrectly reported on INFLUENCE 2.0 as a prediction tool that can be used for treatment decision-making. Using this tool to choose the optimal primary therapy might result in inadequate treatment recommendations, as the underlying model has been designed on a cohort of patients with non-random therapy allocation. Treatment estimates obtained from observational registry data may be biased due to unmeasured confounding and should be very carefully interpreted if used for treatment decisions [6].

More specifically, if one aims to predict potential outcomes in case a patient does or does not receive a specific treatment, several (untestable) assumptions have to be made. The first is that treatment assignment in clinical practice should be similar to the treatment assignment in the cohort that is used for model development. The second is exchangeability, meaning that the tool is able to properly correct for confounding variables. The third is positivity, meaning that the tool should be based on observations of treated and untreated patients for every combination of covariates, to be able to correctly provide predictions for both groups [7]. In general, in observational data there are so many factors that could have influenced treatment decisions – including factors that are not measured – that it is very difficult to provide accurate predictions. Thus, when designing a prediction model that is intended to be used for treatment decision-making, the underlying treatment estimates should be reliable. This can be achieved by using expected treatment effects from well-designed randomised clinical trials, as has been done in the design of the PREDICT tool [1], and the PORTRET tool [3]. Although observational studies – provided that they are properly designed – have been shown to provide similar results as randomised controlled trials in the estimation of treatment effects [8,9], it is still essential to carefully take into account bias due to unmeasured confounding, and to ensure that proper sensitivity analyses are performed that provide insight in the inaccuracy of the predictions [10]. Moreover, the use of a model in clinical practice is recommended only in case these inaccuracies are considered acceptable.

The INFLUENCE 2.0 tool has been developed on patients who already completed treatment. Thus, treatment choices could have been affected by several (unmeasured) factors – unlike treatment assignment in a randomised controlled trial. It is very likely that these factors did not

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only influence therapy allocation but also the observed therapy effect. This does not compromise the model's ability to predict subsequent individual risk estimates, which can consequently be used to determine the most optimal follow-up strategy in a shared decision-making process between patient and care provider. At the same time, it becomes obvious why INFLUENCE 2.0 must not be used as a decision tool for primary breast cancer therapy.

Apart from the fact that the design of a model should be adapted to its intended use, a model should also be validated in the target population to ensure that predictions are accurate enough for that specific population. PREDICT, for example, is intended to be used in women who have had surgery for early invasive breast cancer [1]. This means that the model has been developed on data from patients with these characteristics, making it unreliable to use it on patients with other characteristics, such as women treated with neoadjuvant therapy. To ensure the predictions of the model are accurate, the model always has to be validated on the population in which the model is intended to be used [11,12]. In addition, for users of the tool the methodology should be clearly described according to the TRIPOD guidelines [13], and risk of bias should have been minimised according to the PROBAST tool [14].

1.2. Laws and regulations

Importantly, with the introduction of the medical device regulation (MDR) [15] in the European Union, software that incorporates prediction tools to support clinical decision-making is required to be certified as a medical device before being used in clinical practice. Also, the North-American Food and Drug Agency [16] recently published new guidance clarifying when clinical decision support software should be classified as a medical device. Both PREDICT version 2.2 and INFLUENCE version 2.0 have been certified as a medical device in the EU. In order to certify these tools as a medical device, manufacturers are required to systematically collect evidence regarding a positive benefit/risk ratio, given a specific intended use. Additionally, manufacturers are required to systematically collect, record and analyse relevant data on the quality, performance, and safety of their medical device as part of the post-market surveillance [15]. Based on these data, manufacturers are able to update and improve their devices. Users of the medical device can therefore be confident that the device is safe as long as the use complies with its intended use. Deviating from the intended use is advised against, given that the impact of it on patient outcomes is likely to be unknown and could potentially cause harm. Even if it seems sensible, and may positively provide benefit for patient care, such claims should be substantiated with sufficient clinical data (validation). To overcome the misuse of prediction tools, the intended use of the tool should be very clearly stated.

2. Conclusion

In conclusion, clinicians and patients who are using risk prediction tools in treatment decision-making should be aware of the intended use of the model and its (external) validity in specific patient populations. This claim is substantiated by the MDR. Authors of papers presenting a clinical prediction model should explicitly state the purpose for which the model is intended to be used and clinicians should ensure that the model is validated on the population they are planning to use it for.

Conflict of interest statement

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