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Machine learning to guide the use of adjuvant therapies for breast cancer

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Accurate prediction of the individualized survival benefit of adjuvant therapy is key to making informed therapeutic decisions for patients with early invasive breast cancer. Machine learning technologies can enable accurate prognostication of patient outcomes under different treatment options by modelling complex interactions between risk factors in a data-driven fashion. Here, we use an automated and interpretable machine learning algorithm to develop a breast cancer prognostication and treatment benefit prediction model—Adjutorium—using data from large-scale cohorts of nearly one million women captured in the national cancer registries of the United Kingdom and the United States. We trained and internally validated the Adjutorium model on 395,862 patients from the UK National Cancer Registration and Analysis Service (NCRAS), and then externally validated the model among 571,635 patients from the US Surveillance, Epidemiology, and End Results (SEER) programme. Adjutorium exhibited significantly improved accuracy compared to the major prognostic tool in current clinical use (PREDICT v2.1) in both internal and external validation. Importantly, our model substantially improved accuracy in specific subgroups known to be under-served by existing models. Adjutorium is currently implemented as a web-based decision support tool (https://vanderschaar-lab.com/adjutorium/) to aid decisions on adjuvant therapy in women with early breast cancer, and can be publicly accessed by patients and clinicians worldwide.

Breast cancer is the most common cancer among women globally, with incidence rates varying from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe[1,2]. Although the prognosis of early-stage breast cancer has improved substantially since the introduction of adjuvant endocrine and chemotherapies[3], these treatments need to be used judiciously, with careful balancing of risks and benefits, particularly in patient subgroups where their utility is as yet unclear[4,5]. Over the years, various breast cancer prognostication models have been developed to enable tailored post-surgical therapeutic decisions by predicting the survival profiles of individual patients on the basis of their clinicopathological features. Of these, PREDICT v2.1 (https://predict.nhs.uk) has been the most commonly used worldwide[6–8]. It was recently endorsed by the American Joint Committee on Cancer (AJCC)[9], was accessed through more than one million sessions from 100 cities all over the world in the period spanning from 2011 to 2020 (https://breast.predict.nhs.uk/statistics.html), and is the recommended tool for adjuvant therapy planning in the current National Institute for Health and Care Excellence (NICE) guidelines[10].

However, despite its widespread use, PREDICT v2.1 has been shown to under-perform in specific subgroups of patients, including older patients, patients with tumours over 50 mm, small oestrogen-receptor (ER)-positive tumours or larger ER-negative tumours[11]. Over- or under-estimation of the survival rates within specific patient subgroups could lead to under- or over-treatment, thereby negatively impacting patient outcomes[12–15]. We hypothesize that the limitations of existing tools arise from (1) the lack of flexibility in the underlying Cox regression method predominantly used to develop prognostic models[7,16] and (2) the derivation of models using outdated and relatively modest-sized cohorts where certain subgroups of patients may not be sufficiently represented. Machine learning (ML) technologies that can readily infer complex patterns from data, supported with big data resources, provide the opportunity to address the aforementioned limitations[17,18].

In this Article, we use a state-of-the-art automated ML algorithm, AutoPrognosis[19], to develop and validate Adjutorium, a breast cancer prognostication model that predicts patient survival and adjuvant treatment benefit to guide personalized therapeutic decisions. AutoPrognosis is an open-source software (https://bitbucket.org/mvdschaar/mlforhealthlabpub) that we have developed to automate the deployment of ML in clinical prognostic modelling. The AutoPrognosis algorithm automatically generates a bespoke ML model for the dataset at hand by optimizing an ensemble of ML models (for example, neural networks, random forests and so on) using an advanced Bayesian optimization algorithm, and then uses a symbolic regression algorithm[20] to convert the optimized ensemble into a transparent risk equation that is interpretable to clinicians (Fig. 1). We developed and validated Adjutorium through the AutoPrognosis software using data for nearly one million women in large-scale cohorts that are representative of the UK and US populations.

We trained Adjutorium to predict breast cancer and all-cause mortality without adjuvant therapies by fitting 10 binary classification ensemble models (optimized via AutoPrognosis), where each model was trained to predict patient survival at 10 distinct time horizons spanning from 1 to 10 years from baseline, with 1-year increments. The effects of four adjuvant therapies (chemotherapy, hormone therapy, bisphosphonates and trastuzumab) were incorporated into the model using their estimated relative risk reduction rates from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[21,22]. The input to the model is a set

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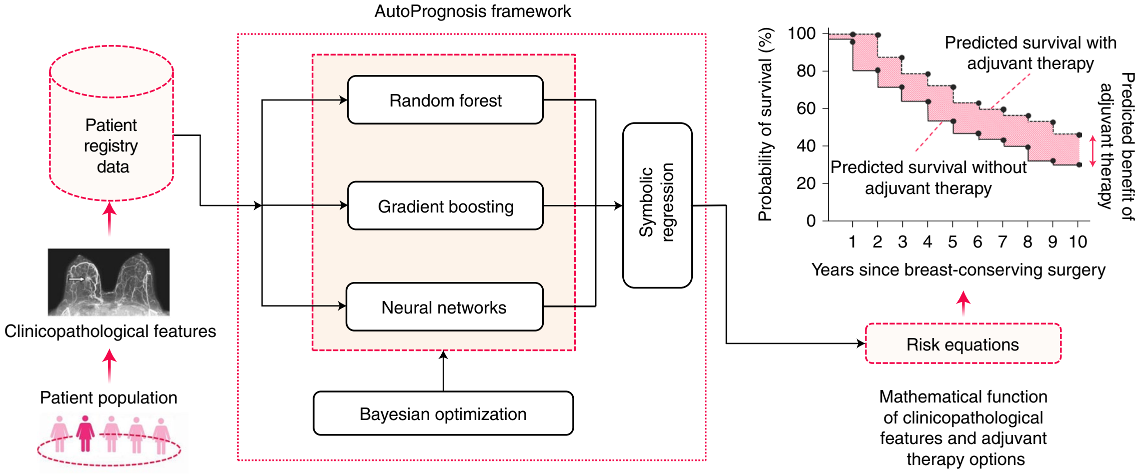

AutoPrognosis framework
Patient registry data
Clinicopathological features
Patient population
Random forest
Gradient boosting
Neural networks
Bayesian optimization
Symbolic regression
Risk equations
Mathematical function of clinicopathological features and adjuvant therapy options
Probability of survival (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
Years since breast-conserving surgery
Predicted survival with adjuvant therapy
Predicted survival without adjuvant therapy
Predicted benefit of adjuvant therapy

Fig. 1 | Schematic depiction of the AutoPrognosis framework. Given patient data, AutoPrognosis uses a Bayesian optimization algorithm to search for the optimal parameters of a collection of ML models and the optimal weight assigned to each model in an ensemble. (Here, we depict random forests, gradient boosting and neural network models as example elements of the ensemble.) After fitting the ensemble model, a symbolic regression algorithm is used to convert the fitted model into a mathematical equation that maps patient variables to predicted risk. The end result is a mathematical equation that computes an individual patient's survival curve with and without a given therapy.

of features for an individual patient, and the outputs are the patient's predicted (breast cancer-specific and all-cause) survival curves under no adjuvant therapy and any combination of the four adjuvant therapies under consideration (inputs and outputs for Adjutorium are visualized in the web application at https://adjutorium-breastcancer.herokuapp.com/). Technical details for the implementation of AutoPrognosis have been described previously[20,23,24]. A brief discussion of AutoPrognosis and a detailed explanation of the training procedure for Adjutorium are provided in the Methods.

Through internal and external validation, we compared the accuracy of Adjutorium in predicting all-cause and breast cancer-specific mortality at 3, 5 and 10 years from baseline with the commonly used PREDICT v2.1 score[7], in addition to an in-house Cox proportional hazards (PH) regression model fitted to the same training cohort used to derive the Adjutorium model. We assessed the discriminative accuracy of all models using the time-dependent area under receiver operating characteristic curve[25] (AUC-ROC), Harrell's concordance index[26] (C-index) and Uno's C-index[27]. Details of the mathematical definitions of each of these metrics are provided in the Supplementary Information. For all evaluations, 95% confidence intervals on the estimated performance metrics were obtained via bootstrapped resampling of the validation data.

Data resources and study cohorts

Patient data for the study were obtained from two cohorts: the UK National Cancer Registration and Analysis Service (NCRAS, $n = 620{,}249$), and the US Surveillance, Epidemiology and End Results programme[28] (SEER, $n = 588{,}735$). NCRAS is the population-based cancer registry for England, and the SEER programme at the National Cancer Institute collects data on cancer diagnoses, treatment and survival for ~30% of the US population. The two databases, combined, hold data for over 1.2 million cases diagnosed between 2000 and 2016. Data were extracted for early breast cancer patients (patients with metastatic cancer were excluded). We extracted patient-level data; patients with multiple primary tumours were represented through their first diagnosis only. The extracted patient-level data comprised standard prognostic factors used in existing prognostic models[7,29,30], including age at diagnosis, mode of detection (screen-detected/symptomatic), ER status, human epidermal growth factor receptor 2 (HER2) status, number of lymph nodes involved, tumour size and histological tumour grade. As this was a large population-based study, with full anonymization of all data, informed consent and ethical approval were not sought.

A total of 395,862 and 571,635 patients met the inclusion criteria for NCRAS and SEER, respectively (Supplementary Fig. 1). Missing data were imputed using the multiple chained equations[31] (MICE) method. Details on the patient inclusion criteria and the steps involved in missing data imputation are provided in the Methods and Supplementary Figs. 2–4, and the patient characteristics are provided in Supplementary Table 1. Patient samples from the NCRAS database were randomly split into two mutually exclusive cohorts: a training cohort of 316,690 patients used for model derivation and an internal validation cohort of 79,172 patients used to evaluate model accuracy. The entire SEER cohort (571,635 patients) was reserved for external validation. The primary outcome of our study was survival from all-cause mortality at 3, 5 and 10 years after surgery for breast cancer. All-cause mortality was further subdivided into breast cancer-specific mortality, which was assessed as a secondary outcome, and mortality due to other causes. Breast cancer-specific mortality was defined as ICD-10 code C.50 listed on the death certificate as a cause of death.

Development of the Adjutorium model for breast cancer prognostication

A high-level illustration for the ML model generated by AutoPrognosis when fitted to the development cohort ($n = 316{,}690$) is provided in Fig. 2. The overall model is based on two ensembles, each comprising four binary classification models[32]: random forest, neural network, gradient boosting and AdaBoost. Individual model weights in the ensemble are provided in the Supplementary Information (the highest weighted model is gradient boosting). One ensemble was trained to predict the risk of breast cancer-specific mortality $P_{\mathrm{bc}}(t)$ at a time horizon t based on all prognostic variables, and the other ensemble was trained to predict the risk of other cause mortality $P_{\mathrm{nbc}}(t)$ based on age. All-cause survival was computed as $P_{\mathrm{bc}}^{\mathrm{HR}}(t) \times P_{\mathrm{nbc}}(t)$, where HR is the risk reduction rate ratio (hazard ratio) of the selected adjuvant therapy (HR = 1 if no treatment is administered). The values of HR for chemotherapy, hormone therapy, bisphosphonates and trastuzumab were obtained from the EBCTCG meta-analyses[21,22].

Through the symbolic regression module in AutoPrognosis (Fig. 1), the ensemble model for $P_{\mathrm{bc}}(t)$ is mathematically represented

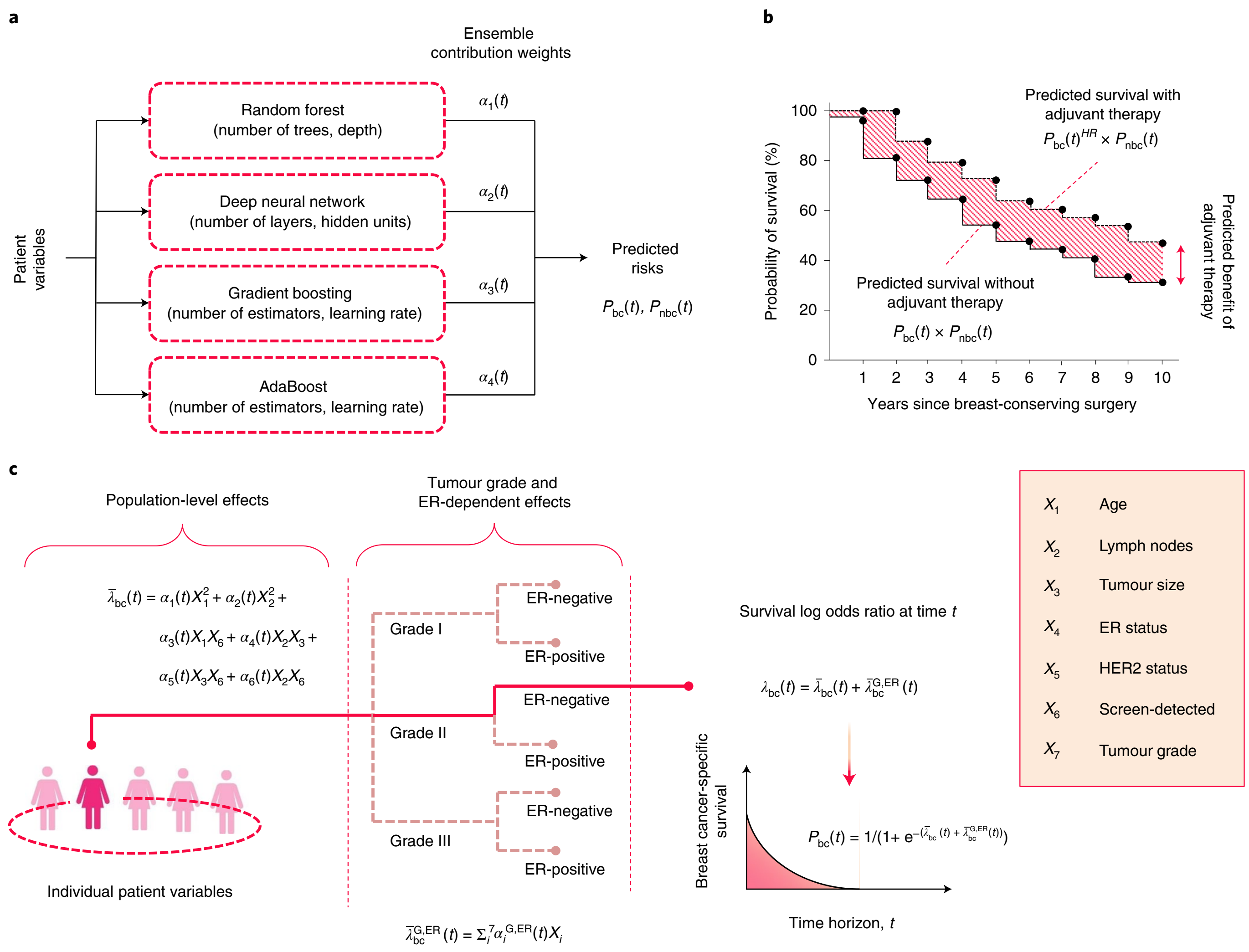

a
Ensemble contribution weights
Patient variables
Random forest (number of trees, depth)
Deep neural network (number of layers, hidden units)
Gradient boosting (number of estimators, learning rate)
AdaBoost (number of estimators, learning rate)
$\alpha_1(t)$
$\alpha_2(t)$
$\alpha_3(t)$
$\alpha_4(t)$
Predicted risks
$P_{bc}(t)$, $P_{nbc}(t)$
b
Probability of survival (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
Years since breast-conserving surgery
Predicted survival with adjuvant therapy
$P_{bc}(t)^{HR} \times P_{nbc}(t)$
Predicted survival without adjuvant therapy
$P_{bc}(t) \times P_{nbc}(t)$
Predicted benefit of adjuvant therapy
c
Population-level effects
$\bar{\lambda}_{bc}(t) = \alpha_1(t)X_1^2 + \alpha_2(t)X_2^2 +$
$\alpha_3(t)X_1X_6 + \alpha_4(t)X_2X_3 +$
$\alpha_5(t)X_3X_6 + \alpha_6(t)X_2X_6$
Individual patient variables
Tumour grade and ER-dependent effects
Grade I
ER-negative
ER-positive
Grade II
ER-negative
ER-positive
Grade III
ER-negative
ER-positive
$\bar{\lambda}^{G,ER}_{bc}(t) = \Sigma_i^7 \alpha_i^{G,ER}(t) X_i$
Survival log odds ratio at time t
$\lambda_{bc}(t) = \bar{\lambda}_{bc}(t) + \bar{\lambda}^{G,ER}_{bc}(t)$
Breast cancer-specific survival
$P_{bc}(t) = 1/(1+ e^{-(\bar{\lambda}_{bc}(t) + \bar{\lambda}^{G,ER}_{bc}(t))})$
Time horizon, t
X_1 Age
X_2 Lymph nodes
X_3 Tumour size
X_4 ER status
X_5 HER2 status
X_6 Screen-detected
X_7 Tumour grade

Fig. 2 | Illustration for the ML model underlying Adjutorium. a,The ensemble model learned by the AutoPrognosis software. The ensemble comprises four basic ML models: random forest, neural network, gradient boosting and AdaBoost. The prediction issued by Adjutorium is a weighted combination of the predictions of the four members of the ensemble. Each model in the ensemble has a set of parameters (listed in parentheses), and an assigned weight $\alpha(t)$ determining its contribution in the final prediction. Both the model parameters and its weight change depending on the prediction horizon t. Separate ensembles are trained to predict breast cancer-specific survival $P_{bc}(t)$ and other cause survival $P_{nbc}(t)$. **b**, The predicted survival curve for an example patient (with and without adjuvant therapy). Here, each prediction horizon (1 to 10 years since diagnosis, with 1-year steps) corresponds to a knot in the survival curve, and each knot is associated with a distinct set of model parameters and contribution weights in the ensemble in **a**. **c**, Risk equations underlying Adjutorium as learned by the symbolic regression module in AutoPrognosis. Given the individual-level variables of a patient, the risk equation evaluates the probability of survival at future time horizons. The log odds ratio for survival at time t comprises two components: (1) a population-level term that models the nonlinear effects of age and number of lymph nodes, in addition to interactions between different variables through six coefficients that are fixed for all patients, and (2) a tumour grade and ER-specific term that evaluates the linear effects of all prognostic factors with coefficients that are specific to every group of patients with the same grade and ER status. Here, we show an example patient with ER-negative cancer and tumour grade 2. The risk equation is a mathematical abstraction for the predictions issued by the ML model in **a**.

in the form of a risk equation that maps patient variables to breast cancer-specific survival functions (Fig. 2c provides a visual depiction of this equation). The risk equation for $P_{bc}(t)$ can be described as follows. For a given patient, breast cancer-related survival probability is given by $P_{bc}(t) = 1/(1 + \exp(-\lambda_{bc}(t)))$, where t is the time horizon at which the survival probability is evaluated. The term $\lambda_{bc}(t)$ can be interpreted as the log odds ratio for survival at time t, and it comprises the following two components:

$$\lambda_{bc}(t) = \underbrace{\bar{\lambda}_{bc}(t)}_{\text{Population} - \text{level}} + \underbrace{\bar{\lambda}^{G,ER}_{bc}(t)}_{\text{Grade} - \text{ER} - \text{specific}}$$

where the first term $\bar{\lambda}_{bc}(t)$ comprises coefficients shared among all patients in the population and includes the nonlinear effects of the age and number of lymph nodes variables, in addition to interaction terms between age, mode of detection, tumour size and number of lymph nodes (Fig. 2c). These interaction terms reflect the impact of the implemented screening policy on patient risks; that is, the coefficients (α_3, α_5, α_6) in Fig. 2c quantify the risk reduction (by early detection of cancer via screening) as a function of the patient's age and tumour spread at time of diagnosis. The second term, $\bar{\lambda}^{G,ER}_{bc}(t)$, includes linear contributions of all prognostic variables, with coefficients specific to subgroups of patients with every possible combination of tumour grade and ER status. The numerical values of the coefficients of $\lambda_{bc}(t)$ are provided in Supplementary Table 9.

The breast cancer-specific mortality risk equation learned by AutoPrognosis demonstrates that our ML approach identified new interactions that were not incorporated in previous models[7], namely the interactions between tumour grade and all other variables. These results are in agreement with new approaches to molecular subtyping that use both receptor status and tumour grade to categorize breast cancer into several conceptual molecular classes (for example, luminal A and B subtypes) that have different prognoses and (potentially) different responses to specific therapies[33]. Thus, the interpretable risk equation learned by AutoPrognosis not only ensures model transparency, but also provides insights into the discovery of new breast cancer subtypes. The interpretable risk equation did not exhibit a significant performance loss compared to the raw ensemble model learned by AutoPrognosis (Supplementary Table 12).

For benchmark purposes, the PREDICT v2.1 score and a standard Cox PH model fit on the same training data as Adjutorium were also assessed for comparison. Consistent with previous studies[7], we fitted two separate Cox models, with different baseline hazards for ER-positive and ER-negative cancer to capture the interactions between ER status and other prognostic variables. We included an age-squared term to allow for nonlinear effects of baseline age at diagnosis on breast cancer mortality. Tumour size and number of lymph nodes were both coded as continuous variables. Coefficients of the fitted Cox PH model are provided in Supplementary Table 2.

Accuracy of the Adjutorium model

Of 395,862 eligible patients in NCRAS, the mean age of breast cancer diagnosis was 61 years, with two million person-years of total follow-up (median follow-up time of 5.2 years) within the cohort. The SEER cohort included 571,635 eligible patients with a mean age of diagnosis of 61 years, and a total 3.2 million person-years of follow-up (median follow-up time of 5.7 years). During follow-up, 83,139 and 139,225 deaths were recorded in NCRAS and SEER, respectively, of which 53,143 (64%) and 59,585 (43%) cases were breast cancer-related. Overall five-year survival rates from breast cancer were 90% and 86% in SEER and NCRAS, respectively.

Discriminative accuracy. Adjutorium uniformly outperformed PREDICT v2.1 and the conventional Cox PH model in predicting all-cause and breast cancer-specific mortality, both when validated internally within NCRAS and externally within the SEER cohort (Table 1). The improvements were achieved with respect to all discriminative accuracy metrics and all time horizons under study.

In internal validation, Adjutorium predicted 10-year all-cause mortality with an AUC-ROC accuracy of 0.815 (95% CI: 0.813–0.817), compared with 0.777 (95% CI: 0.768–0.772) by PREDICT v2.1 and 0.775 (95% CI: 0.773–0.777) by the Cox PH model. Similar performance gains were achieved over the other time horizons and with respect to the C-index statistic (Table 1). The improvements in accuracy achieved by Adjutorium were even more significant in predicting breast cancer-specific mortality, with an AUC-ROC of 0.825 (95% CI: 0.823–0.827) for 10-year outcomes, compared with 0.730 (95% CI: 0.727–0.733) by PREDICT v2.1 and 0.783 (95% CI: 0.781–0.785) by the Cox PH model. The fact that the accuracy improvements were more significant in the secondary outcome is not surprising, because all of the variables included in the model were breast cancer-related. In all experiments, the performance improvements by Adjutorium compared to the most competitive baseline (with respect to all metrics) were statistically significant, with P values less than 0.001.

Adjutorium generalized well to the external validation cohort, with similar accuracy improvements for both the primary and secondary outcomes (Supplementary Table 4). With respect to 10-year all-cause mortality, Adjutorium achieved an AUC-ROC of 0.790 (95% CI: 0.787–0.793), compared to 0.756 (95% CI: 0.753–0.759) by PREDICT, 0.631 (95% CI: 0.628–0.634) by NPI and 0.778 (95% CI: 0.771–0.785) by the Cox PH model. Similar gains were achieved over the other time horizons (Supplementary Table 4). For prediction of 10-year breast cancer-specific mortality, Adjutorium achieved an AUC-ROC of 0.803 (95% CI: 0.800–0.806), compared to 0.744 (95% CI: 0.741–0.747) by PREDICT, 0.768 (95% CI: 0.765–0.771) by NPI and 0.775 (95% CI: 0.770–0.780) by the Cox PH model.

Importantly, Adjutorium outperformed the Cox PH model fitted to the same development cohort, reflecting the ‘gain from modelling’, that is, the gain achieved by using flexible ML models instead of standard regression. On the other hand, the gain achieved by the Cox PH model compared to PREDICT v2.1 in external validation reflects the ‘gain from information’, that is, the gain achieved by using large-scale, representative data that enhance the accuracy and generalizability of the fitted models to other cohorts that might entail different demographic structure and outcomes.

Subgroup analysis. The accuracy improvements achieved by Adjutorium were consistent across all subgroups of patients stratified by age, HER2 status, ER status and tumour grade (Table 2). Improvements were greater in subgroups that are poorly served by current prognostic tools; indeed, the accuracy gains achieved by Adjutorium relative to PREDICT v2.1 were higher in elderly patients (age > 65 years at diagnosis) and patients with ER-negative and HER2-negative breast cancer. This is probably due to the fact that our ML-based risk equation captured nuanced interactions and nonlinear patterns that were not incorporated in existing prognostic tools (Fig. 2c).

Sensitivity analyses and calibration performance. We conducted various tests to evaluate the robustness of our results. First, we tested the robustness of Adjutorium to time–cohort effects, and internal validation on sub-cohorts stratified by diagnosis dates from 2005 to 2016 showed that the accuracy gains by Adjutorium are achieved for all diagnosis years, except for 10-year all-cause mortality in more recent diagnosis years where both models perform similarly (Fig. 3). (This is mainly because recent cohorts do not have sufficient follow-up.) Moreover, we applied internal and external validation on sub-cohorts with complete data and missing data to test the robustness of Adjutorium to data missingness; the model performed well in cases with complete and missing data, outperforming other models by similar margins in both analyses (Supplementary Table 6). When validated on 21,164 patients (in the internal validation cohort) with complete data on all variables, the AUC-ROC accuracy of Adjutorium with respect to 10-year breast cancer-specific mortality was 0.811 (95% CI: 0.0.808–0.814), whereas this was 0.783 (95% CI: 0.780–0.786) for PREDICT v2.1. When validated on 57,996 patients with missing data on one or more variables, the AUC-ROC accuracy of Adjutorium was 0.829 (95% CI: 0.0.827–0.831), and it was 0.728 (95% CI: 0.725–0.731) for PREDICT v2.1.

Adjutorium was well-calibrated across study cohorts, displaying better calibration with observed outcomes than PREDICT v2.1 (Supplementary Fig. 6). In internal validation, we found that PREDICT v2.1 substantially over-estimated the risk of both all-cause and breast cancer-related mortality at 10-year follow-up. In external validation, PREDICT v2.1 over-estimated the risk of breast cancer-related mortality, but was relatively more conservative in predicting all-cause mortality. Although Adjutorium was noted to under-estimate mortality in patients who were at high risk for breast cancer and all-cause mortality, this is unlikely to impact clinical decision-making, as these individuals are likely to be well beyond the decision threshold for improvement with treatment. Moreover, patients in this risk subgroup comprised only 6% of the overall population.

Impact on adjuvant therapy decisions

To assess the clinical benefit of using Adjutorium to support decisions regarding adjuvant therapies, we compared Adjutorium predictions of treatment benefit to those of PREDICT v2.1 and to the

Table 1 | Discriminative accuracy with respect to the primary and secondary outcomes

Internal validation cohort (NCRAS, $n = 79,172$)

Time horizon	Metric (95% CI)	Adjutorium	Cox PH	PREDICT	Adjutorium	Cox PH	PREDICT
		All-cause mortality			Breast cancer-specific mortality		
3 years	H. C-index	0.782 (0.781–0.783)	0.755 (0.753–0.757)	0.746 (0.745–0.747)	0.809 (0.808–0.810)	0.773 (0.771–0.775)	0.739 (0.738–0.740)
	U. C-index	0.755 (0.753–0.757)	0.735 (0.733–0.737)	0.708 (0.705–0.711)	0.764 (0.762–0.766)	0.732 (0.730–0.734)	0.701 (0.700–0.702)
	AUC-ROC	0.818 (0.816–0.820)	0.795 (0.793–0.797)	0.785 (0.783–0.787)	0.849 (0.847–0.851)	0.817 (0.816–0.818)	0.766 (0.764–0.768)
5 years	H. C-index	0.787 (0.785–0.789)	0.755 (0.753–0.757)	0.757 (0.755–0.759)	0.808 (0.807–0.809)	0.774 (0.773–0.775)	0.749 (0.748–0.750)
	U. C-index	0.755 (0.753–0.757)	0.733 (0.732–0.734)	0.718 (0.716–0.720)	0.767 (0.765–0.769)	0.737 (0.735–0.739)	0.709 (0.707–0.711)
	AUC-ROC	0.816 (0.814–0.818)	0.773 (0.771–0.775)	0.775 (0.773–0.777)	0.835 (0.833–0.837)	0.796 (0.794–0.798)	0.755 (0.753–0.757)
10 years	H. C-index	0.773 (0.771–0.775)	0.759 (0.757–0.760)	0.772 (0.770–0.774)	0.790 (0.788–0.792)	0.778 (0.777–0.779)	0.751 (0.749–0.753)
	U. C-index	0.745 (0.743–0.747)	0.735 (0.734–0.736)	0.734 (0.732–0.736)	0.756 (0.754–0.758)	0.736 (0.734–0.738)	0.715 (0.714–0.716)
	AUC-ROC	0.815 (0.813–0.817)	0.775 (0.773–0.777)	0.770 (0.768–0.772)	0.825 (0.823–0.827)	0.783 (0.781–0.785)	0.730 (0.727–0.733)

External validation cohort (SEER, $n = 571,635$)

Time horizon	Metric (95% CI)	Adjutorium	Cox PH	PREDICT	Adjutorium	Cox PH	PREDICT
		All-cause mortality			Breast cancer-specific mortality		
3 years	H. C-index	0.752 (0.749–0.755)	0.746 (0.745–0.747)	0.737 (0.736–0.738)	0.797 (0.795–0.799)	0.763 (0.760–0.766)	0.764 (0.762–0.766)
	U. C-index	0.743 (0.741–0.745)	0.735 (0.734–0.736)	0.698 (0.696–0.700)	0.755 (0.750–0.760)	0.727 (0.722–0.732)	0.721 (0.715–0.727)
	AUC-ROC	0.771 (0.770–0.772)	0.773 (0.770–0.776)	0.762 (0.761–0.763)	0.823 (0.820–0.826)	0.792 (0.787–0.797)	0.784 (0.782–0.786)
5 years	H. C-index	0.758 (0.757–0.759)	0.744 (0.742–0.746)	0.743 (0.741–0.745)	0.796 (0.794–0.798)	0.769 (0.766–0.772)	0.765 (0.763–0.767)
	U. C-index	0.736 (0.732–0.740)	0.732 (0.725–0.739)	0.709 (0.707–0.711)	0.760 (0.755–0.765)	0.722 (0.714–0.730)	0.735 (0.730–0.740)
	AUC-ROC	0.777 (0.775–0.779)	0.763 (0.759–0.767)	0.755 (0.753–0.757)	0.815 (0.813–0.817)	0.784 (0.782–0.786)	0.775 (0.772–0.778)
10 years	H. C-index	0.749 (0.746–0.752)	0.741 (0.737–0.745)	0.751 (0.750–0.752)	0.778 (0.776–0.780)	0.764 (0.761–0.767)	0.765 (0.763–0.767)
	U. C-index	0.735 (0.730–0.740)	0.738 (0.732–0.744)	0.728 (0.726–0.730)	0.746 (0.741–0.751)	0.728 (0.720–0.736)	0.738 (0.734–0.742)
	AUC-ROC	0.790 (0.787–0.793)	0.778 (0.771–0.785)	0.756 (0.753–0.759)	0.803 (0.800–0.806)	0.775 (0.770–0.780)	0.744 (0.741–0.747)

CI, confidence interval; H. C-index and U. C-index, Harrell and Uno concordance indices, respectively.

observed decisions of multidisciplinary teams (MDTs) obtained from the NCRAS database. To this end, we followed decision thresholds currently used for decision-making with PREDICT within the UK, recommending chemotherapy if a patient's 10-year net survival benefit from treatment is predicted to be greater than 5%[34] and no adjuvant chemotherapy if treatment benefit is <3%. The decisions when survival benefit was predicted to be 3–5% were made on a case-by-case basis; no formal guidelines exist regarding these at present. We compared 5- and 10-year survival among patients where MDT decision-making regarding treatment (extracted from the registry data) had been concordant with Adjutorium with survival among patients where this had been disconcordant. We also conducted a similar comparison with PREDICT v2.1, examining average survival of patients with disconcordant predictions of treatment benefit between the algorithms. Finally, we assessed how many additional patients who had died of breast cancer within 10 years would have been assigned to treatment by Adjutorium relative to treatment assignment by MDTs and PREDICT v2.1.

The average benefits of chemotherapy predicted by Adjutorium and PREDICT v2.1 in all study cohorts were found to be significantly different (t-test, $P < 0.001$). Figure 4 visualizes the disconcordance between treatment decisions informed by Adjutorium and PREDICT v2.1, in addition to the observed MDT decisions in light of the patients' 10-year outcomes. In both the internal and external validation cohorts, Adjutorium and PREDICT v2.1 disagreed on treatment decisions for 19% of the patient population (Fig. 4a).

Table 2 | Subgroup-level discrimination with respect to breast cancer-specific 10-year outcomes

Internal validation cohort (NCRAS)

			Adjutorium			PREDICT v2.1		
	No. of cases	No. of observed deaths	AUC-ROC	TP	FP	AUC-ROC	TP	FP
Age at diagnosis (yr)								
ER-positive								
30–65	21,302	2,314	0.791	1,658	5,142	0.773	1,607	5,171
>65	13,115	3,774	0.824	3,026	2,767	0.779	2,915	2,937
ER-negative								
30–65	10,417	2,440	0.729	1,615	2,634	0.666	1,595	3,043
>65	4,861	2,090	0.785	1,458	730	0.700	1,626	1,202
HER2-positive								
30–65	11,894	2,390	0.717	1,563	3,157	0.682	1,535	3,299
>65	4,388	1,940	0.767	1,370	733	0.671	1,449	1,131
HER2-negative								
30–65	19,825	2,363	0.816	1,749	4,286	0.797	1,749	4,898
>65	13,588	3,924	0.825	2,970	2,443	0.763	3,088	3,433
Grade I								
30–65	4,942	146	0.752	101	1,262	0.739	103	1,580
>65	2,608	382	0.816	273	423	0.758	290	683
Grade II								
30–65	6,472	1,772	0.753	1,218	1,286	0.720	1,291	1,754
>65	6,920	2,891	0.693	2,120	1,737	0.684	2,165	1,824
Grade III								
30–65	5,935	2,820	0.730	2,061	1,210	0.630	1,785	1,249
>65	4,503	2,577	0.662	1,921	942	0.613	1,370	652

External validation cohort (SEER)

			Adjutorium			PREDICT v2.1		
	No. of cases	No. of observed deaths	AUC-ROC	TP	FP	AUC-ROC	TP	FP
Age at diagnosis (yr)								
ER-positive								
30–65	74,732	18,374	0.798	14,286	20,034	0.799	14,941	19,544
>65	38,226	14,290	0.806	10,527	6,174	0.800	10,688	6,212
ER-negative								
30–65	61,070	17,594	0.768	11,552	11,138	0.727	10,829	12,948
>65	25,812	11,564	0.797	7,894	3,378	0.766	9,053	4,571
HER2-positive								
30–65	1,467	1,467	–	–	–	–	–	–
>65	958	958	–	–	–	–	–	–
HER2-negative								
30–65	134,335	34,501	0.766	24,155	33,485	0.745	23,441	27,704
>65	63,080	24,896	0.791	17,383	9,978	0.769	16,206	8,243
Grade I								
30–65	18,073	1,517	0.736	1,025	4,139	0.725	960	5,575
>65	10,643	1,850	0.740	1,110	2,146	0.700	983	1,849
Grade II								
30–65	68,596	13,180	0.718	9,691	12,477	0.712	6,736	11,387
>65	63,009	13,397	0.700	9,433	21,828	0.700	7,584	12,329
Grade III								
30–65	62,560	21,157	0.728	13,754	12,029	0.730	13,456	11,885
>65	30,630	10,531	0.700	6,360	7,829	0.720	7,724	7,820

FP and TP denote false-positive and true-positive cases, respectively. Empty cells correspond to subgroups with no enough patients for estimating FP and TP.

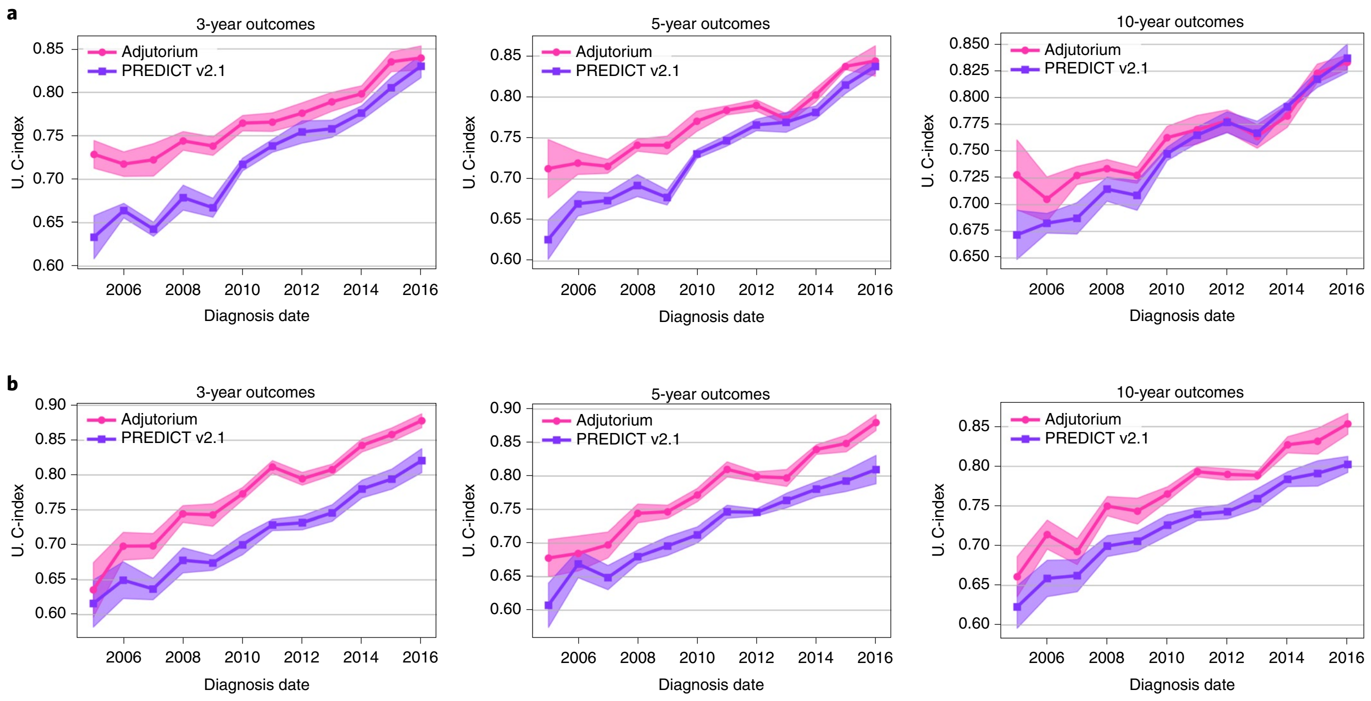


Fig. 3 | Discriminative accuracy evaluated in sub-cohorts of patients stratified by diagnosis date. a, Discriminative accuracy with respect to all-cause mortality. **b**, Discriminative accuracy with respect to breast cancer-specific mortality. U. C-index, Uno concordance index.

The population of patients that were recommended a treatment by Adjutorium but not by PREDICT or MDTs (populations P2 and P4 in Fig. 4) had a higher than average mortality rate at 10 years. An average 10-year mortality of 28% is consistent with a benefit of >5%, suggesting that, on average, this treatment subgroup would have benefited from treatment.

On the contrary, the population of patients that were not recommended a treatment by Adjutorium, but were recommended chemotherapy by PREDICT or the MDT decisions exhibited a 10-year mortality rate less than that of the populational average. A 10-year mortality of 18% in the group disconcordantly assigned to treatment by PREDICT suggests average treatment benefit in the range of 2.4%. This indicates that treatment decisions informed by Adjutorium are less likely to over- or under-treat patients. Compared to historical decisions made by MDTs, Adjutorium can potentially improve treatment decisions for 25% of the patient population (13% who are under-treated and 12% who are potentially over-treated).

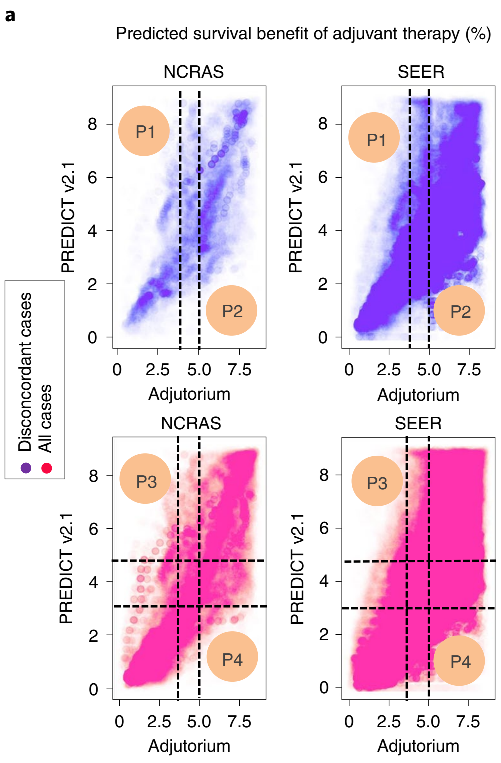
Discussion

We have developed and validated Adjutorium, a ML-based tool for predicting the individualized benefit of adjuvant therapies in breast cancer. Involving data from nearly one million individuals with breast cancer from the United Kingdom and the United States, this is one of the largest studies of its kind. We found that Adjutorium substantially outperforms one of the most widely used standards for clinical decision-making and, critically, is generalizable to distinct clinical settings across multiple nationally representative cohorts.

Although several prognostication methods are available for supporting clinical decisions regarding adjuvant therapies in breast cancer, they have well-recognized limitations, particularly in terms of their accuracy in certain subgroups and their generalizability to other populations. We find that Adjutorium outperforms existing clinical decision support tools in terms of accuracy, as well as calibration to observed outcomes, across all patient groups. Additionally, it shows substantially improved performance in subgroups where existing clinical decision support tools are known perform poorly (for example, older women with early cancer, ER-negative breast cancer) suggesting that using Adjutorium to support clinical decisions may lead to better treatment decisions and potentially better outcomes in these subgroups. In contrast with other existing tools, Adjutorium is robust to missing data and is able to make accurate predictions even when information on some of the prognostic factors is not available. This is an important advance, making our model more generalizable to settings where data on patients may be incomplete. Importantly, we observe lower 10-year mortality among patients where MDT decisions are concordant with Adjutorium predictions. This has important implications for clinical decision support, and highlights the utility of tools such as Adjutorium for prognostication to potentially drive better patient outcomes.

We find that Adjutorium not only outperforms PREDICT v2.1, but also a Cox PH model fit on the same training cohort. This suggests that gains in performance are achieved not only due to a larger representative set for training the models, but also due to the flexible nature of the ML algorithms applied. Our fitted model does not make any assumptions about the linearity of the patient risks as a function of prognostic factors, or the proportionality of hazards over time. Additionally, it is able to infer interactions and nonlinear associations in a data-driven fashion, as is evident through the interpretable risk equations describing the ML model.

To improve accessibility and general use, we also provide an easy-to-use online tool for breast cancer prediction (http://www.vanderschaar-lab.com/adjutorium/) based on the Adjutorium model, where patient features can be easily input to a visualization tool that depicts the patient survival time under different treatment options. This portal allows clinicians to work with patients to make important decisions regarding adjuvant therapy treatments in a personalized context. We thus provide an important clinical tool for breast cancer treatment management to be used within the UK, and globally. Moreover, we provide an open-source software for the AutoPrognosis system, which enables other researchers to easily re-fit the model as more data become available. Because our approach is automated, it would help clinical researchers update



b

Population P1: untreated by Adjutorium, treated by MDT. MR: NCRAS = 0.85, SEER = 0.88

	Age (yr)	Lymph nodes, *N*	Tumour size (mm)	Tumour grade I (%)	ER-positive (%)	HER2-positive (%)	Screen-detected (%)
NCRAS (*n* = 9,904)	55.7	2.5	22	10	69	41	65
SEER (*n* = 73,866)	57.7	1.9	22	18	80	13	–

Population P2: treated by Adjutorium, untreated by MDT. MR: NCRAS = 1.13, SEER = 1.08

	Age (yr)	Lymph nodes, *N*	Tumour size (mm)	Tumour grade I (%)	ER-positive (%)	HER2-positive (%)	Screen-detected (%)
NCRAS (*n* = 10,345)	63.0	5.6	28	2.7	59	37	16.7
SEER (*n* = 101,861)	57.3	1.2	24	1.8	41	3	–

Population P3: untreated by Adjutorium, treated by PREDICT. MR: NCRAS = 0.92, SEER = 0.75

	Age (yr)	Lymph nodes, *N*	Tumour size (mm)	Tumour grade I (%)	ER-positive (%)	HER2-positive (%)	Screen-detected (%)
NCRAS (*n* = 5,096)	60.0	7.9	23	6	43	47	34
SEER (*n* = 12,105)	60.0	5.9	37	2	29	15	–

Population P4: treated by Adjutorium, untreated by PREDICT. MR: NCRAS = 1.20, SEER = 1.60

	Age (yr)	Lymph nodes, *N*	Tumour size (mm)	Tumour grade I (%)	ER-positive (%)	HER2-positive (%)	Screen-detected (%)
NCRAS (*n* = 9,285)	58.2	1.9	25	1.9	66	20	41
SEER (*n* = 99,389)	55.4	0.7	20	2.5	54	3.5	–

Fig. 4 | Comparison between therapeutic decisions informed by Adjutorium and PREDICT v2.1. a, Disconcordance between the different models. **b**, Characteristics of the patients in disconcordant cases. Differences in mortality ratios across the different models were statistically significant ($P < 0.001$ with a ratio (logarithmic) *t*-test). MR, mortality ratio (defined as the ratio between the 10-year mortality rate in the selected population and that of the overall population).

the model as different aspects of the healthcare system change over time (for example, introduction of novel adjuvant therapies), without the need to involve experts in making new modelling choices and decisions repeatedly for every new update. Moreover, the symbolic regression module can communicate these model updates to clinicians by highlighting changes in model coefficients and newly discovered interactions and nonlinearity, which makes the entire process transparent.

We acknowledge limitations of our model, which include the retrospective nature of our study, which makes it difficult to assess changes in patient outcomes when using Adjutorium relative to existing tools. Another limitation is that our model does not predict outcomes such as recurrence, and currently does not incorporate multigene assays or other gene expression-based predictive information. In addition, we had no access to progesterone receptor (PR) status in the development cohort, so this was not included in our prognostic variables. Although also not considered in previous scores, such as PREDICT and the Nottingham Prognostic Index, we believe that that incorporating PR status into prognostic modelling may prove beneficial in future studies. Additional prognostic variables and genetic-based markers can be easily incorporated into our model using our automated approach for feature processing, which can optimize variable selection and dimensionality reduction algorithms to handle high-dimensional clinical and genetic variables.

Another limitation is that Adjutorium does not explicitly derive treatment effects in a data-driven fashion, instead using estimates from meta-analyses on clinical trials. We also acknowledge limitations of the data used to derive our model, including the lack of complete information on bisphosphonates and trastuzumab in the NCRAS derivation cohort, lack of information on treatments other than chemotherapy in SEER and incomplete coding of chemotherapy variables in SEER. Moreover, in both the NCRAS and SEER datasets, there were only indicators of whether chemotherapy was administered to each patient, without specification of the type of regimen used (second- or third-generation regimens). In our analysis, we made the conservative choice of using the HRs for the more prevalent and slightly less efficacious regimen to adjust for survival times in training data to avoid overestimating survival for untreated patients. Given our accurate survival predictions for untreated patients, the effects of both second-generation regimens (taxane-containing regimen without an anthracycline) and third-generation regimens (containing both taxanes and anthracyclines) can be incorporated within Adjutorium in real-world deployment, without the need for re-training (Supplementary Table 8).

In summary, we have developed and validated Adjutorium, a flexible and generalizable ML-based tool for clinical decision support in breast cancer treatment. Our work suggests that using Adjutorium to support decisions made by MDTs around adjuvant therapy could potentially improve patient outcomes relative to existing decision support tools, across distinct clinical settings. Further work in prospective longitudinal cohort studies will be needed to quantify and realize these benefits in practice.

Methods

Data sources and patient inclusion criteria. From NCRAS, we included patients who were diagnosed after 1 January 2005. This extra inclusion criteria in NCRAS was necessary as the missingness of the HER2 status variable was predictive of outcome (patients with HER2 missing have worse outcomes, on average). Because the missingness rate of HER2 status before 2005 was very high, including patients with complete HER2 information with diagnosis dates before 2005 would cause a bias in the survival outcomes. From both datasets, we included patients who were aged 30–90 years at diagnosis. Specific age data were not available for patients less than 30 years of age in NCRAS, so these were excluded. We also excluded patients with missing data on more than four variables (<10% of all participants) and a small number of patients who were outliers for tumour size (>90-mm tumour) and number of positive lymph nodes (>50). A total of 395,862 and 571,635 patients met the inclusion criteria in NCRAS and SEER, respectively. We did not include Ki67 status, as this was not available for the vast majority of patients in NCRAS and has already been shown to have poor predictive power[35,36].

The extracted NCRAS dataset contained complete information on which patients were treated with chemotherapy and hormone therapy, but did not include information on other adjuvant therapies, such as targeted anti-HER2 agents. The release of complete treatment information was in violation of the data anonymization constraints imposed by the NCRAS data-sharing policy. In addition, information on other adjuvant therapies was only routinely recorded for patients diagnosed in more recent years. Thus, to validate our model on data with complete treatment information, we acquired an anonymized supplementary NCRAS dataset of 17,804 patients diagnosed in 2013, with complete information on chemotherapy, hormone therapy, immunotherapy, CDK4/6 inhibitors, PARP inhibitors, trastuzumab and bisphosphonates. We denote this dataset NCRAS-2. Details on the patient characteristics and validation results for the NCRAS-2 sub-cohort are provided in Supplementary Tables 2 and 11. The NCRAS-2 sub-cohort (including all patients diagnosed in 2013 within the NCRAS dataset) comprised a total of 17,804 eligible patients with a median follow-up time of 5.38 years. Among these, 84.72% received chemotherapy, 19.49% received hormone therapy, 22.43% received trastuzumab and 3% received bisphosphonates.

Missing data imputation. A limitation of existing models has been their dependence on complete case analysis and a lack of flexibility to incorporate missing variables. Our analysis suggested that missingness was highly informative[37] (log-rank test for difference in five-year survival between patients with complete data and one or more missing variable, $P < 0.001$). In this context, including only patients with complete data is likely to affect model generalizability. Therefore, in the interest of generalizability, we opted to impute any missing data using data available on other variables. For all study cohorts, we imputed missing data using the model-based MICE[31] method. We created 10 imputed datasets and pooled the predictions of all models under study using Rubin's rule[38]. Details regarding imputation are provided in the Supplementary Information.

Model development. *Automated machine learning.* We derived the Adjutorium model using the AutoPrognosis[19] framework, an open-source software (https://bitbucket.org/mvdschaar/mlforhealthlabpub) that we have developed to automate the deployment of ML in clinical prognostic modelling. As it is automated, AutoPrognosis can be used by clinical researchers to build prognostic models tailored to a given dataset without the need for in-depth knowledge of ML, clearing one of the most important hurdles to using these approaches in routine clinical practice[39]. Furthermore, this framework overcomes the 'black-box' nature of ML models by converting the trained model into an interpretable and transparent risk equation.

AutoPrognosis automatically constructs an optimized prognostic model fit to the dataset at hand by tuning the parameters of an ensemble of state-of-the-art ML pipelines; each pipeline comprises an imputation algorithm, a feature processing algorithm, a ML prediction model and a calibration algorithm. (Here, we deactivate the feature pre-processing module as the number of prognostic variables involved in model development is relatively small.) The overall Adjutorium model was constructed by fitting 10 binary classification ensemble models (optimized via AutoPrognosis) to predict outcomes at 10 distinct knots (time horizons spanning from 1 to 10 years from baseline, with 1-year increments). The AutoPrognosis algorithm creates this ensemble by tuning the parameters of the ML models using an advanced Bayesian optimization technique, then combining these tuned models using Bayesian model averaging[19].

To convert the ML ensemble (created through Bayesian optimization) into a transparent model of risk, AutoPrognosis uses a symbolic regression methodology to automatically convert the trained ensemble model into an understandable mathematical equation that links patient variables to predicted outcomes. It does so using a search technique that optimizes parameterized symbolic expressions comprising combinations of univariate Meijer *G*-functions[20]. Survival curves were created by smoothing the coefficients for the symbolic expressions describing the model predictions at the 10 knots via cubic spline interpolation.

Cox model. A standard Cox PH model fit on the same data as used for Adjutorium was also assessed for comparison. Consistent with previous methods[7], we applied two separate models, with different baseline hazards for ER-positive and ER-negative cancer. We included an age-squared term to allow for nonlinear effects of baseline age at diagnosis on breast cancer mortality. Tumour size and number of lymph nodes were both coded as continuous variables. Separate models where fit to each of the 10 imputed datasets, and the resulting predictions of the 10 models (evaluated on validation data) were pooled using Rubin's rule.

The coefficients of the Cox PH model fitted to the training cohort (with breast cancer-specific outcomes) and averaged over the 10 imputed datasets are provided in Supplementary Table 1. The in-sample Harrell's concordance index of the pooled predictions for ER-negative cancer was 0.72, whereas that for ER-positive cancer was 0.80. HER2 status qualitatively interacts with ER status to modify the risk of breast cancer mortality (HR for HER2-positive tumours is 0.73 (95% CI: 0.69–0.77) for patients with ER-positive tumours, and 1.24 (95% CI: 1.20–1.28) for patients with ER-negative tumours). This indicates that HER2-positive status is associated with reduced risk for mortality in ER-negative cancer, but associates with relatively worse prognosis in ER-positive cancer.

Model training. Patient samples from the NCRAS database were randomly split into two mutually exclusive cohorts: a training cohort of 316,690 patients used for model derivation and an internal validation cohort of 79,172 patients used to evaluate model accuracy. The entire SEER cohort (571,635 patients) was reserved for external validation. We trained Adjutorium using the NCRAS data to predict breast cancer and all-cause mortality without adjuvant therapies by adjusting survival times for treatment effects to create a counterfactual 'untreated' survival cohort. Estimated survival time in the absence of treatments was calculated as

$$S_{\mathrm{bc}}^{T=0} = S_{\mathrm{bc}}^{T=1} \times \mathrm{HR} \tag{1}$$

where S_{bc} represents the uncensored survival time for each individual, T is the indicator for treatment and HR is the hazard ratio associated with a specific treatment based on the EBCTCG meta-analysis[21,22]. This is consistent with previous approaches used to create adjusted counterfactual survival times in crossover trials[40]. The same procedure was applied to the Cox PH model. The Adjutorium model incorporates four treatments: chemotherapy, hormone therapy, bisphosphonates and trastuzumab. Other therapies, such as immunotherapy, targeted PARP and CDK4/6 inhibitors are primarily used for patients with metastatic cancer with no sufficient data on their usage as adjuvant therapies, so we did not include them in our model[41].

Model validation. We conducted internal and external validation of Adjutorium within the NCRAS validation cohort ($n = 79{,}172$) and the SEER cohort ($n = 571{,}635$), respectively. In addition, we also validated our model in the NCRAS-2 sub-cohort, which comprised 3,560 patients with complete treatment information. We validated predicted outcomes in the original unadjusted cohort, incorporating treatment effects for patients that had received therapy. Using this approach allowed us to evaluate the predictive accuracy of overall survival without treatment and improvement of survival with treatment. As breast cancer mortality and mortality from other causes are competing causes, overall survival probability from all causes was calculated as

$$P_{\mathrm{all}}(t) = P_{\mathrm{bc}}(t) \times P_{\mathrm{nbc}}(t) \tag{2}$$

Here, $P_{\mathrm{all}}(t)$, $P_{\mathrm{bc}}(t)$ and $P_{\mathrm{nbc}}(t)$ represent overall survival, survival from breast cancer and survival from other non-breast cancer-related causes at time horizon t, respectively. We test the independence between causes in Supplementary Fig. 5. For individuals on adjuvant therapy, $P_{\mathrm{bc}}(t)$ was calculated as a function of survival without treatment $P_{\mathrm{bc}}^{T=0}(t)$ (as predicted by the trained model) and the effect of treatment as

$$P_{\mathrm{bc}}^{T=1}(t) = \left(P_{\mathrm{bc}}^{T=0}(t)\right)^{\mathrm{HR}} \tag{3}$$

Statistical analysis. *Discriminative accuracy.* We compared the discriminative accuracy of Adjutorium in predicting all-cause and breast cancer-specific mortality at 3, 5 and 10 years from baseline relative to PREDICT v2.1[7] and the in-house Cox PH model fitted to the NCRAS training cohort. For the NCRAS-2 cohort, we only evaluated discriminative accuracy for three- and five-year outcomes because patients in this cohort were diagnosed in 2013, so the maximum follow-up time in this cohort was less than six years. We assessed the discriminative accuracy of Adjutorium using the time-dependent AUC-ROC[25], Harrell's C-index[26] and Uno's C-index[27]. Details on the mathematical definitions of each of these metrics are provided in the Supplementary Information. For all evaluations, 95% confidence intervals were obtained using bootstrapped resampling of the validation data.

Calibration accuracy. We evaluated the calibration curves of Adjutorium by comparing the predicted risk of mortality with observed risk at the time horizons of interest. For each time horizon, we divided the risk ranges predicted by Adjutorium into 10 quantiles and, within each quantile, we estimated the observed risk in the corresponding patient samples using a Kaplan–Meier estimator[42]. Calibration curves were evaluated by plotting the predicted risks by Adjutorium on the x axis and the corresponding observed risk on the y axis.

Sensitivity analyses. To examine the robustness of Adjutorium to missingness, we validated its performance separately on individuals with complete data and those with at least one missing variable. (In Supplementary Table 6, we also validate Adjutorium on individuals with different numbers of missing variables, and individuals with each variable missing.) Moreover, to assess the robustness of Adjutorium to time–cohort effects, due to changes in patient management and survival over time, we compared its discriminative accuracy with that of PREDICT in subsets of patients diagnosed within 1-year windows spanning from 2005 to 2016.

Subgroup analyses. We validated Adjutorium within specific patient subgroups stratified by age, ER status, HER2 status, tumour size and tumour grade. We specifically assessed the performance of Adjutorium relative to PREDICT v2.1 in patients aged more than 65 years, patients with larger tumours (>50 mm) and patients with negative ER status. Error counts (true-positive and false-positive cases, corresponding to the number of cases misclassified) in each subgroup were obtained through decision thresholds that maximize the Youden J-statistic for each model.

Data availability

The dataset used to derive and internally validate the model was obtained from the National Cancer Registration and Analysis Service. These data are held by Public Health England. Information on how to access the data is available at http://ncin.org.uk/collecting_and_using_data/data_access. The dataset used for external validation was obtained from the Surveillance, Epidemiology and End Results programme, which can be accessed at https://seer.cancer.gov/seertrack/data/request/.

Code availability

The code for the AutoPrognosis software is available at https://bitbucket.org/mvdschaar/mlforhealthlabpub.

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Author contributions

A.M.A., D.G., A.L.H., J.R. and M.v.d.S. designed the study. A.M.A. and M.v.d.S. led the development of the automated ML model. A.M.A., D.G., A.L.H. and M.v.d.S. led the writing. D.G., A.L.H., J.R. and M.v.d.S. led the analysis and interpretation of the data. A.M.A. and D.G. provided statistical and analytical support. All authors read and approved the final draft of the manuscript. All authors are accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

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