A DREAM Challenge to Build Prediction Models for Short-Term Discontinuation of Docetaxel in Metastatic Castration-Resistant Prostate Cancer

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Purpose Docetaxel has a demonstrated survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC); however, 10% to 20% of patients discontinue docetaxel prematurely because of toxicity-induced adverse events, and the management of risk factors for toxicity remains a challenge.

Patients and Methods The comparator arms of four phase III clinical trials in first-line mCRPC were collected, annotated, and compiled, with a total of 2,070 patients. Early discontinuation was defined as treatment stoppage within 3 months as a result of adverse treatment effects; 10% of patients discontinued treatment. We designed an open-data, crowd-sourced DREAM Challenge for developing models with which to predict early discontinuation of docetaxel treatment. Clinical features for all four trials and outcomes for three of the four trials were made publicly available, with the outcomes of the fourth trial held back for unbiased model evaluation. Challenge participants from around the world trained models and submitted their predictions. Area under the precision-recall curve was the primary metric used for performance assessment.

Results In total, 34 separate teams submitted predictions. Seven models with statistically similar area under precision-recall curves (Bayes factor ≤ 3) outperformed all other models. A postchallenge analysis of risk prediction using these seven models revealed three patient subgroups: high risk, low risk, or discordant risk. Early discontinuation events were two times higher in the high-risk subgroup compared with the low-risk subgroup. Simulation studies demonstrated that use of patient discontinuation prediction models could reduce patient enrollment in clinical trials without the loss of statistical power.

Conclusion This work represents a successful collaboration between 34 international teams that leveraged open clinical trial data. Our results demonstrate that routinely collected clinical features can be used to identify patients with mCRPC who are likely to discontinue treatment because of adverse events and establishes a robust benchmark with implications for clinical trial design.

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INTRODUCTION

Despite decades of research and advances in treatment, the long-term prognosis of metastatic castration-resistant prostate cancer (mCRPC) remains poor.[1] Docetaxel was the first cytotoxic drug to improve survival and quality of life in patients with mCRPC[2,3] and has remained a standard first-line chemotherapy for the treatment of mCRPC. Although several clinical trials have confirmed the population-level survival and palliative benefits of docetaxel,[4,5] a significant fraction of patients do not respond to docetaxel, and within approximately 8 months, nearly all patients become resistant to treatment or stop therapy.[2,3] Of patients who initially experience a response to docetaxel, 10% to 20% prematurely discontinue as a result of toxicity-induced adverse events (AEs) that include anemia, (febrile) neutropenia, fatigue, GI complications, and neuropathies.[6-8] Managing the risk factors for toxicity is a major challenge, as they may diminish a patient's quality of life without extending it.

As docetaxel-based chemotherapy continues to play an important role in the treatment of mCRPC and, more recently, hormone-sensitive metastatic prostate cancer,[9] it is important to prospectively identify patients for whom a docetaxel-based regimen is likely to be poorly tolerated and to result in AE and potentially early treatment failure. In

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particular, such knowledge could be used to iden-
tify patients for pre-emptive clinical interventions
and/or supportive care before chemotherapy or to
direct patients to alternative treatment regimens.
In addition, establishing quantitative benchmarks for
identifying patients who are at high risk for early
treatment discontinuation can be used to facilitate
more efficient clinical trial design. Prognostic models
to predict overall patient survival in mCRPC have
been previously described[10-14]; however, whether
early treatment discontinuation as a result of adverse
events can be predicted on the basis of a patient's
baseline clinical characteristics remains an unan-
swered question. Within the clinical trial data used
in this study, approximately 10% of patients with
mCRPC discontinued treatment within 3 months
of starting docetaxel. Given this low percentage of
patients, access to a sufficiently powered data set
is a major factor in being able to address the
question of whether treatment discontinuation
can be predicted.

Here, we report the results from the Prostate Cancer
DREAM (Dialogue for Reverse Engineering Assess-
ment and Methodology) Challenge, the first crowd-
sourced competition in mCRPC. The aim of this
challenge was to determine whether baseline clinical
characteristics can be used to predict patients who
will discontinue their docetaxel-based treatment be-
cause of adverse events. This challenge builds on the
open clinical trial data initiative of Project Data
Sphere, LLC, a nonprofit initiative of the CEO Round-
table on Cancer's Life Consortium. The comparator
arms of four phase III clinical trials with a total of
2,070 patients were collected, cleaned, annotated,
and made public, removing the privacy and legal
barriers for open data access. During a 5-month
period, 34 teams from around the world worked
independently to address the challenge, which
resulted in novel models for the prediction of dis-
continuation and identification of clinical variables
that are associated with treatment discontinuation.
We also demonstrate how clinical trial design can be
optimized through the use of these models. Finally,
we present a new paradigm for addressing chal-
lenges in biomedical clinical informatics through a
postchallenge, community-based collaboration be-
tween challenge organizers and participating teams
to evaluate and refine risk prediction models.

PATIENTS AND METHODS

Trial Selection, Patient Population, and Data Processing

Data used in this challenge were compiled on the
basis of provider-deidentified comparator arms
of four phase III prostate cancer clinical trials

(ASCENT2[15]: n = 476, 105 patients discontinued
docetaxel within 3 months as a result of AE or pos-
sible AE; VENICE[16]: n = 598, 51 discontinued pa-
tients; MAILSAIL[17]: n = 526, 41 discontinued
patients; and ENTHUSE 33[18]: n = 470, 49 discon-
tinued patients). All trials were randomized and
shared similar inclusion and exclusion criteria. Eligible
patients included those with progressive mCRPC, no
previous chemotherapy, and an Eastern Cooperative
Oncology Group (ECOG) performance status of 0 to 2.
Detailed inclusion and exclusion criteria of each trial
can be found in Guinney et al[10] and the Data
Supplement. In total, data used in this challenge
consisted of 2,070 patients with first-line mCRPC
who were treated with a docetaxel-based treatment
regimen. A total of 129 baseline clinical variables
were compiled for each trial with details of data
curation provided in the Data Supplement.

Patient Discontinuation

The outcome variable—treatment discontinuation—
was derived from two factors: reason for treatment
discontinuation (Data Supplement) and the time
from treatment initiation to discontinuation. Dis-
continuation of treatment was evaluated for the
first 3 months of treatment or the first four cycles
(12 weeks) of treatment in a 10-cycle regimen
(3 weeks per cycle). Patients were labeled as
discontinued if, and only if, they discontinued treat-
ment as a result of AE or possible AE within 3 months
(91.5 days) after beginning treatment. The number
and percentage of patients who were assigned to a
detailed list of categories are provided in the Data
Supplement.

Challenge Design, Scoring, and Evaluation

The challenge was hosted and managed on the
free, cloud-based Synapse platform.[19]

ASCENT2, VENICE, and MAINSAIL data sets—
clinical features and outcome—were combined to
create the training data set (n = 1,600). The out-
come variable for the ENTHUSE 33 data (n = 470)
was withheld and used as an independent valida-
tion set to evaluate model prediction performance.
Teams were tasked with developing models to
predict early discontinuation of docetaxel as a
result of AE or possible AE (Data Supplement).
A team's prediction was a ranked list of risk scores
for all patients in the ENTHUSE 33 data; teams
were allowed two submissions. Risk scores that
were submitted by each team were evaluated and
ranked by using the area under the precision-
recall curve (AUPRC).[20] (NOTE. Precision = pos-
itive predictive value and recall = sensitivity.)
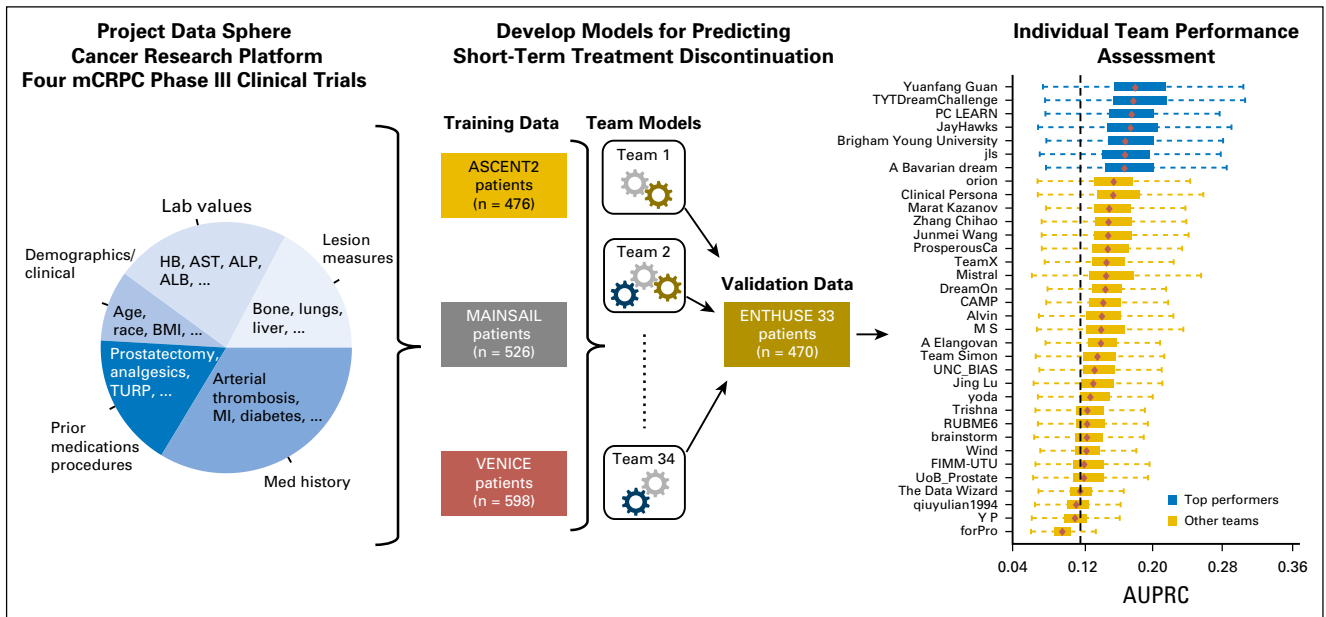AUPRC was selected over the area under the

Fig 1. Study design. Data were acquired from Project Data Sphere Cancer Research Platform and centrally curated by the organizing team to create a standardized data set across the four studies. Three of the studies (ASCENT2, VENICE, and MAINSAIL) were selected as training sets, and a fourth data set (ENTHUSE 33) was withheld as a validation set. Teams submitted risk scores for evaluation in the validation set, which were scored and ranked by using the area under the precision-recall curve (AUPRC). The vertical dashed line in the rightmost panel represents the bootstrap estimate of the fraction of discontinuation events in the ENTHUSE33 dataset. (NOTE. Precision = positive predictive value, recall = sensitivity.) ALB, albumin; ALP, alkaline phosphatase; BMI, body mass index; HB, hemoglobin; mCRPC, metastatic castration-resistant prostate cancer; MI, myocardial infarction; TURP, transurethral resection of the prostate.

receiver operating characteristic curve (AUROC) to take into account the highly skewed distribution of classes (10% to 20% of patients discontinuing treatment). AUPRC, unlike AUROC, emphasizes the ability of a model to predict patients who discontinue treatment (true positives) and is recommended for imbalanced data.[20-22]

The following criteria were used to determine the top teams and models: prediction performance was significantly better than a random prediction model,[23] and performance was statistically indistinguishable compared with the model that achieved the highest AUPRC score. One-sided *P* values were computed as the probability of observing an AUPRC under the null distribution that was at least as large as the AUPRC obtained for a given team, then corrected for multiple hypothesis testing.[24] To assess whether consecutively ranked models were distinguishable in terms of their AUPRC score, the Bayes factor[25,26] was computed between each model and the top-ranked model. Submissions with a Bayes factor of < 3 were determined to be statistically indistinguishable as suggested by Kass and Raftery.[26] The Bayes factor method generates a bootstrapped performance distribution between two models, where a Bayes factor of 3, for example, means that the first method outperformed the second method at a 3-to-1 ratio. Additional details can be found in the Data Supplement.

Risk scores submitted by each team were also subjected to a cumulative lift chart analysis (Data Supplement). For each team and model, we summarized the results by computing the area under

the lift ratio curve and the lift ratio among patients with the highest predicted risk of early treatment discontinuation (top 5%, 10%, and 20%).

Postchallenge Community Collaboration to Improve Patient Risk Predictions

After the completion of the challenge, hierarchical clustering was performed over the ranked patient risk scores to find a consensus pattern among the top-performing teams to identify patients who were at high or low risk of developing AEs. Unsupervised hierarchical clustering was performed by using the Manhattan distance and Ward agglomerative clustering. In addition to concordant high- and low-risk patients, we found a group of patients without any consensus risk stratification across the models, which is referred to as the discordant group. The elbow method was used to determine the number of clusters for patients; we calculated the within-group variation for different numbers of clusters, ranging from 1 to 10. The optimal number of clusters was determined at the point where the variation begins to flatten, arriving at three clusters.

To improve patient risk predictions, an ensemble-based prediction model[27] was generated as the weighted average of the top seven models (Data Supplement). To calculate a team's weight, each team trained their models on 70% of randomly sampled patients from the ASCENT2, VENICE, and MAINSAIL trials, then predicted risk scores for the remaining 30% of patients. This team performance established team weights. Finally, this ensemble approach was applied to the ENTHUSE 33 data and compared with individual model performances.

Table 1. Summary of Selected Baseline Clinical Characteristics Across Trials

Characteristic	Training Set			Validation Set
	ASCENT2 (n = 476)	MAINSAIL (n = 526)	VENICE (n = 598)	ENTHUSE 33 (n = 470)
Age, years				
18-64	111 (23.3)	171 (32.5)	219 (36.6)	160 (34.0)
65-74	211 (44.3)	246 (46.8)	254 (42.5)	217 (46.2)
≥ 75	154 (32.4)	109 (20.7)	125 (20.9)	93 (19.8)
ECOG PS*				
0	220 (46.2)	257 (48.9)	280 (46.8)	247 (52.6)
1	234 (49.2)	247 (47.0)	291 (48.7)	223 (47.4)
2	22 (4.6)	20 (3.8)	27 (4.5)	0 (0.0)
Metastasis				
Liver*	5 (1.1)	58 (11.0)	60 (10.0)	64 (13.6)
Bone*	345 (72.5)	439 (83.5)	529 (88.5)	470 (100)
Lungs	8 (1.7)	74 (14.1)	88 (14.7)	56 (11.9)
Lymph nodes	163 (34.2)	298 (56.7)	323 (54.0)	208 (44.3)
Analgesic use				
No	338 (71.0)	347 (66.0)	419 (70.1)	339 (72.1)
Yes	138 (29.0)	179 (34.0)	179 (29.9)	131 (27.9)
LDH, U/L				
1st quantile	176	174	NA	181
Median	202	210	NA	213
3rd quantile	250	267	NA	287
Missing	13 (2.7)	1 (0.2)	596 (99.7)	5 (1.1)
PSA, ng/mL				
1st quantile	24.2	32.2	30.8	33.6
Median	68.8	84.9	90.8	99.6
3rd quantile	188.4	271.2	260.6	236.8
Missing	1 (0.2)	4 (0.8)	6 (1)	12 (2.6)
Hemoglobin, g/dL*				
1st quantile	11.6	11.5	11.7	11.3
Median	12.6	12.7	12.7	12.5
3rd quantile	13.6	13.7	13.5	13.5
Missing	3 (0.6)	10 (1.9)	0 (0)	4 (0.9)
Albumin, g/L*				
1st quantile	NA	41	38	40
Median	NA	43	42	43
3rd quantile	NA	45	45	46
Missing	476 (100)	1 (0.2)	16 (2.7)	2 (0.4)
Alkaline phosphatase, U/L*				
1st quantile	80	81	85	98
Median	113	124	135	155
3rd quantile	213	265	270	328

Table 1. Summary of Selected Baseline Clinical Characteristics Across Trials (continued)

Characteristic	Training Set			Validation Set
	ASCENT2 (n = 476)	MAINSAIL (n = 526)	VENICE (n = 598)	ENTHUSE 33 (n = 470)
AST, U/L				
1st quantile	20	19	20	20
Median	24	24	25	25
3rd quantile	31	31	33	33
Missing	4 (0.8)	1 (0.2)	8 (1.3)	3 (0.6)

NOTE. Data are presented as No. (%) or quantiles (1st, median, or 3rd). Albumin for ASCENT2 was missing, and LDH tests for VENICE were almost all missing.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NA, not available; PSA, prostate-specific antigen.
*Variables that show significant difference between training and validation data sets (K-S test or Chisq test $P < .05$).

Clinical Trial Model Simulations

A simulation study was conducted to quantify the benefit of incorporating patient risk for early treatment discontinuation into patient selection in terms of the sample size requirements for clinical trials (Data Supplement). We assumed a balanced two-arm randomized controlled trial—1-to-1 random assignment between treatment and control arms—and survival time as the end point. We used data from the ENTHUSE 33 trial to inform simulation parameters, then simulated 100 independent data sets in 10,000 patients using the survsim package in R.[28] These data were used to estimate the sample size that was required to detect a survival difference (hazard ratio [HR], 1.3, 1.4, …, 2.0) between the groups at 80% statistical power and a false positive rate of 5%. Patients who were identified as being at risk for early discontinuation were excluded from random assignment, assuming different accuracies (0%, 25%, 50%, 75%, and 100%) of the baseline prediction models at identifying true cases of early discontinuation.

Data and Method Availability

Clinical trial data can be accessed at Project Data Sphere, LLC.[29] Method write-ups, code, and predictions for all teams are reported in the Data Supplement. Challenge documentation, overall results, scoring scripts, and data dictionary can be found at Synapse.[30]

RESULTS

The overall challenge design is illustrated in Fig 1. Across all trials, a total of 129 baseline clinical variables were made available. Although the majority of baseline clinical variables were consistent across the four trials, notable differences in the distribution of binary clinical features—primarily lesion sites—were observed (Table 1 and Data Supplement). The

Fig 2. Rate and frequency of treatment discontinuation across trials. (A) Trial-specific cumulative incidence functions for treatment discontinuation as a result of adverse events or possible adverse events (solid lines) and death (dotted lines). (B) Fraction of patients with metastatic castration-resistant prostate cancer who discontinued treatment ≤ 3 months after initiation because of adverse events or possible adverse events.
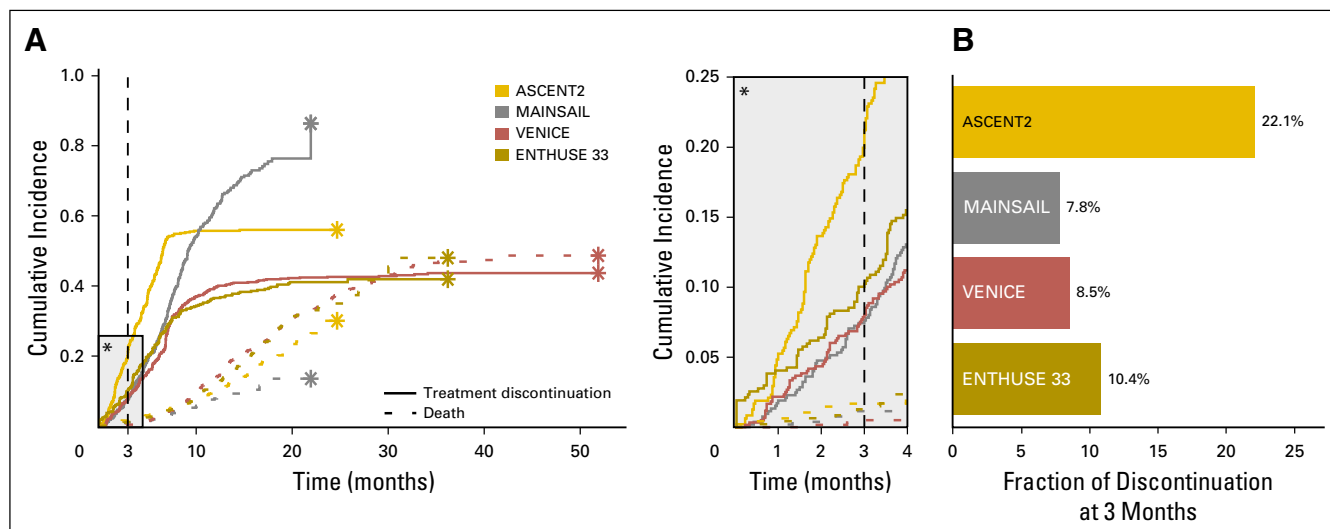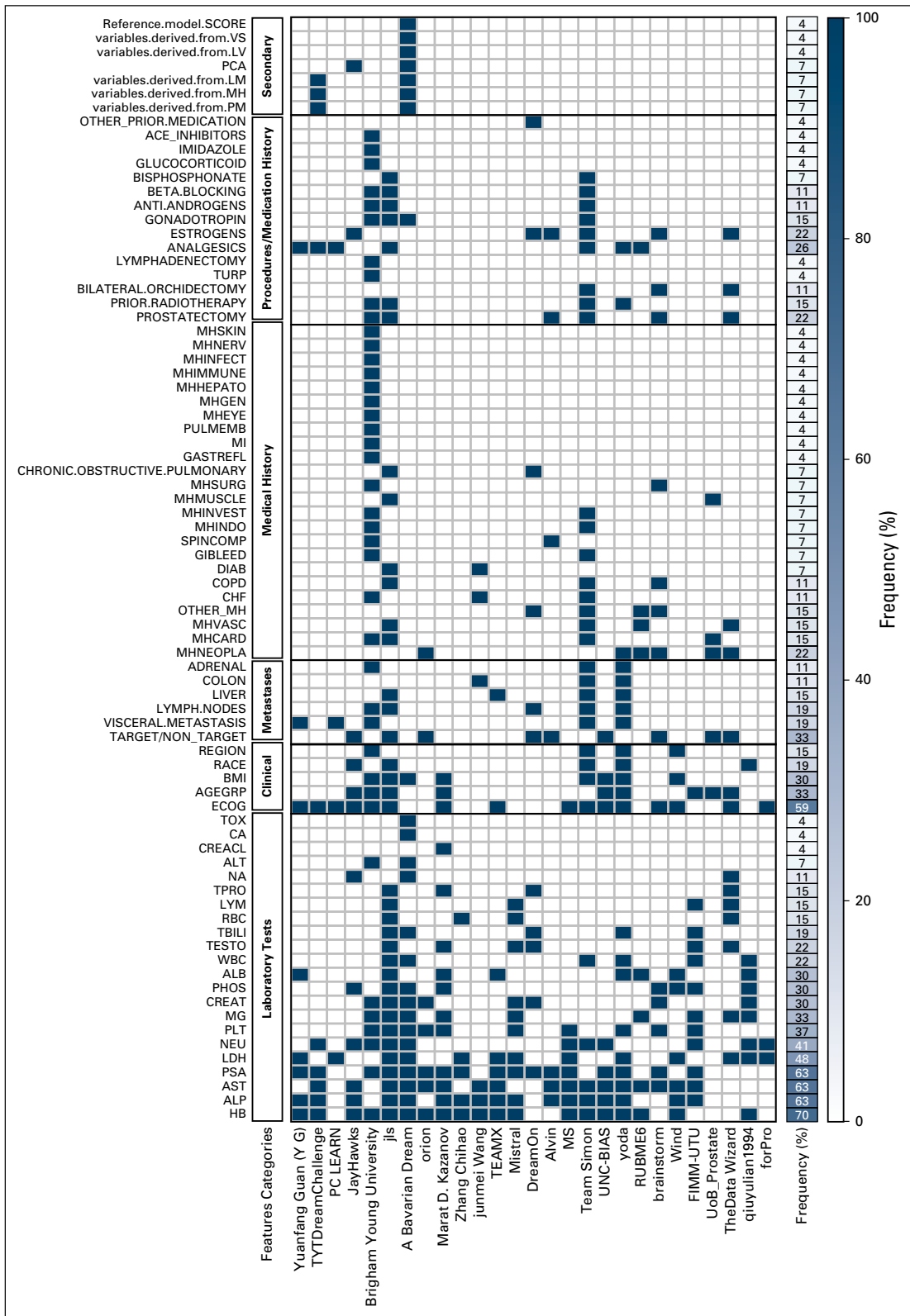
Fig 3. Most frequent clinical features used across all prediction models. Abbreviated terms are provided in the Data Supplement.

frequency of early discontinuation events was similar between training and validation sets (12% v 10% of patients, respectively), but varied across individual trials (Fig 2).

A total of 34 independent, international teams made 61 submissions to the challenge. A summary of each team's approach is provided in the Data Supplement. Among teams that responded
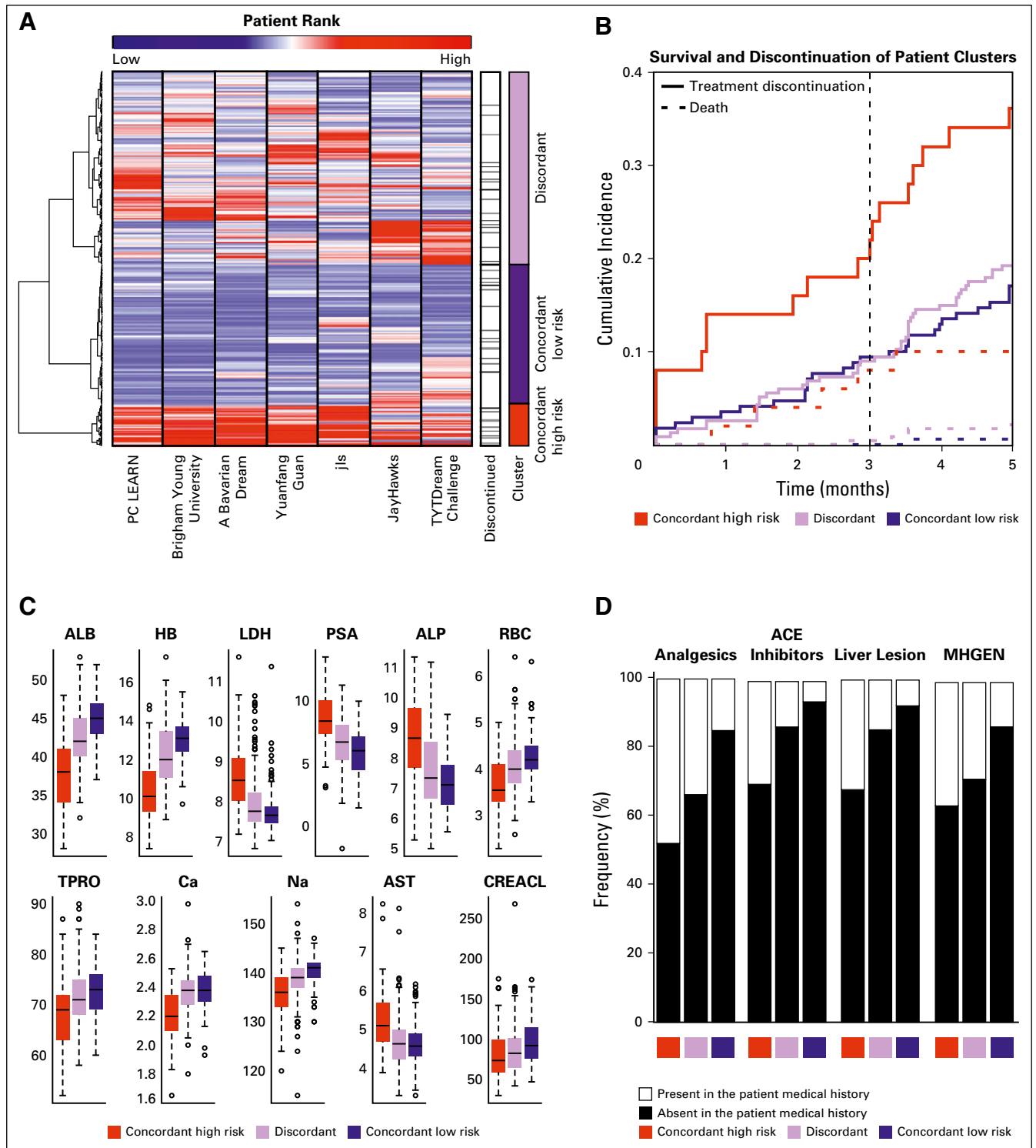
Fig 4. Meta-analysis of risk scores computed by the seven top-performing teams. (A) Hierarchical clustering heatmap of patients in the ENTHUSE 33 validation data set (n = 470) on the basis of their normalized ranked risk score, computed across the seven top-performing teams. (B) Kaplan-Meier curves, stratified by event type—that is, death or treatment discontinuation—across the three identified patient subgroups. (C) Distribution of baseline laboratory variables found to be significantly different between the three patient subgroups. (D) Distribution of baseline prior medical and medication variables found to be significantly different between the three patient subgroups. ACE, angiotensin-converting enzyme; ALB, albumin; ALP, alkaline phosphatase; Ca, calcium; CREACL, creatinine clearance; HB, hemoglobin; LDH, lactate dehydrogenase; MHGEN, medical history: general disorders and administration site conditions; Na, sodium; PSA, prostate-specific antigen; TPRO, total protein.

to a postchallenge survey, the five most common clinical features used in prediction models were hemoglobin (HB), alkaline phosphatase (ALP), AST, prostate-specific antigen (PSA), and ECOG performance status (Fig 3).

For evaluating team performance on the task of predicting patient discontinuation using imbalanced data (10% to 20% discontinue rate), we chose AUPRC (additional details provided in Patients and Methods and the Data Supplement). Across all submissions, AUPRC ranged between 0.088 and 0.178 (AUROC ranged between 0.55 and 0.60), with 0.104 representing the expected AUPRC for a random prediction model, which is reflective of the 10% rate of discontinuation observed in the ENTHUSE 33 trial (Fig 2 and Data Supplement). Of the 34 teams, 30 performed better than random, with seven teams performing significantly better than a random model (adjusted $P < .10$). In rank order, teams Yuanfang Guan, TYTDreamChallenge, PC LEARN, JayHawks, Brigham Young University, jls, and A Bavarian Dream achieved AUPRCs that were within a Bayes factor of 3 (Data Supplement); thus, these seven teams were identified as the challenge top performers.

A cumulative lift chart analysis was performed on each submission to provide context for their associated risk predictions. Across the top seven models, the average measure of 1.34 represents a 34% improvement in predicting short-term discontinuation compared with no risk predictions being made (Data Supplement). Restricting the above analysis to the top 10% of patients with the highest predicted risk revealed that models improved the identification of early discontinuation events by a factor of two, on average, when compared with no risk predictions being made (Data Supplement).

To compare the risk predictions generated by the top seven performers, we hierarchically clustered the ranked patient risk scores, which resulted in three groups of patients: patients who were consistently predicted to be at high risk of early discontinuation (concordant high risk; n = 50), patients with a consistent low risk of early discontinuation (concordant low risk; n = 170), and patients with discordant risk scores (discordant risk; n = 234 patients; Fig 4A). A nearly two-fold increase in cumulative incidence of early discontinuation was observed when the high-risk group was compared with the low-risk and discordant groups (Fig 4B). At 3 months post-treatment, 26% of patients in the concordant high-risk group discontinued docetaxel compared with only 9% in the

low-risk and discordant groups. The competing risk—that is, death—was considerably elevated in the concordant high-risk group compared with the low-risk and discordant groups.

A comparison of baseline characteristics across the three groups revealed 11 statistically significant laboratory values (adjusted $P < .05$), including albumin, HB, lactate dehydrogenase, PSA, sodium, RBC, ALP, calcium, AST, creatinine clearance, and total protein (Fig 4C). In addition, ECOG performance status and metastatic liver lesions differed significantly between the concordant high-risk and low-risk groups (adjusted $P < .05$). Use of analgesics and angiotensin-converting enzyme inhibitors was significantly elevated among patients in the high-risk group (48% and 30%, respectively) compared with those in the low-risk group (15% and 5%, respectively; Fig 4D). A similar trend was observed in the frequency of patients with liver metastasis; liver lesions were reported for only 8% of patients in the concordant low-risk group compared with 32% in the high-risk group.

Results from previous DREAM Challenges have demonstrated that integrating predictions from multiple top-performing teams produces robust and often better results than the top individual teams.[31-33] Motivated by these previous results and the modest correlation of risk scores across the top performers (Data Supplement), we developed a weighted average ensemble prediction model using the top seven models, with weights empirically determined (Data Supplement). Application of the ensemble-based model to the ENTHUSE 33 trial resulted in an AUPRC of 0.230 (AUROC, 0.599; Fig 5A). The ensemble-based model outperformed the top individual performers the majority of times (73% to 95% across the top seven models), and achieved a Bayes factor > 3 compared with all but one challenge submission (team Yuanfang Guan, Bayes factor, 2.75; Data Supplement). A cumulative lift chart analysis of risk predictions that were computed from the ensemble-based model demonstrated a 14% improvement over the top challenge submission (Fig 5B). Additional analysis revealed a statistically significant increase in the area under the lift ratio curve at 20% ($P < .01$; Fig 5C).

To evaluate our ensemble-based prediction model within the broader context of clinical trial design, we conducted a simulation study to compare the sample size requirements of trials that incorporate risk estimates for early treatment discontinuation as a patient inclusion criterion for the treatment
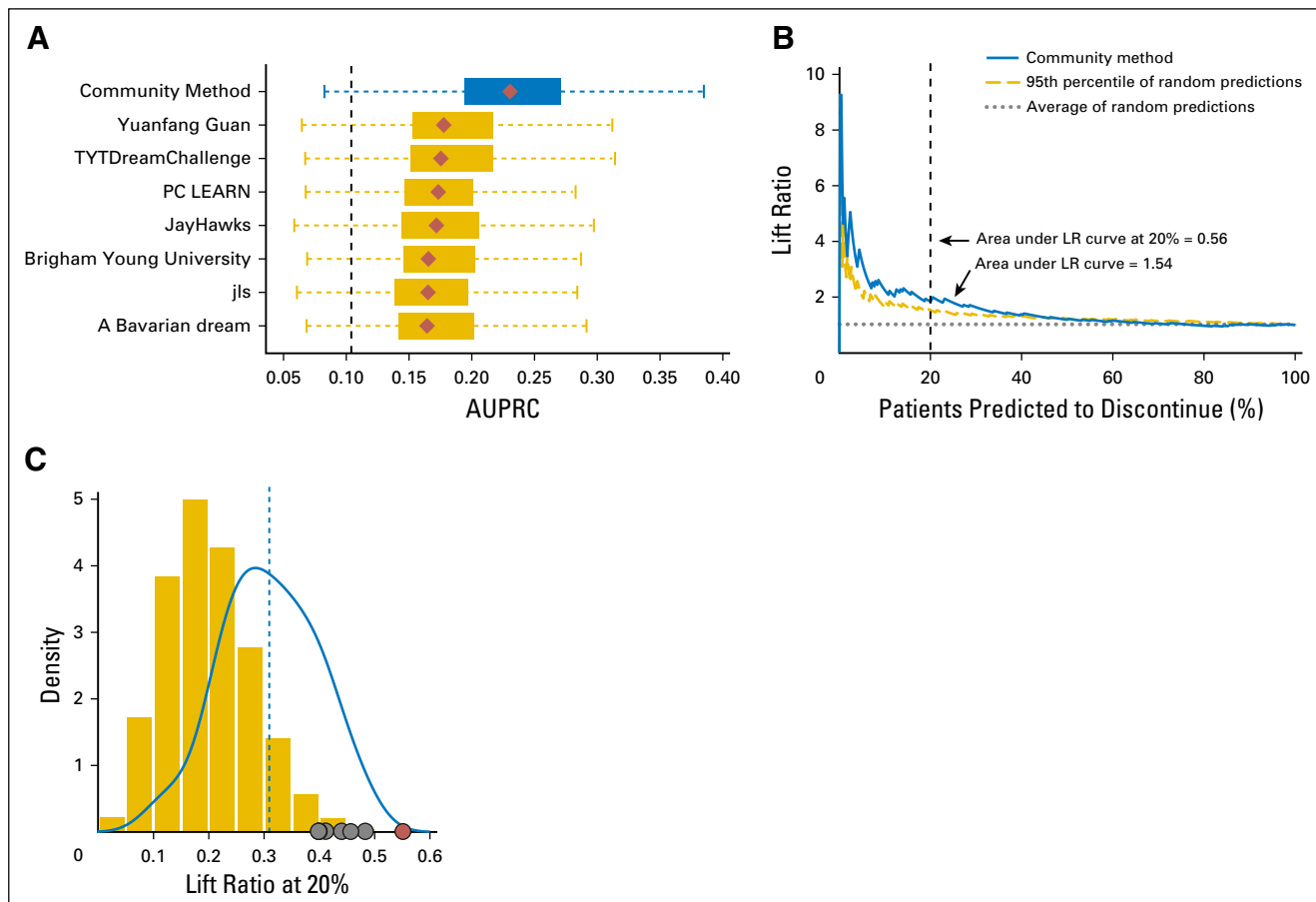
Fig 5. Performance of the postchallenge ensemble-based prediction model. (A) Area under the precision-recall curve (AUPRC) computed within the ENTHUSE 33 data set for the ensemble-based prediction model, along with the models developed by the seven top-performing teams. Diamonds represent the observed AUPRCs, and horizontal boxplots reflect the empirical distribution of a model's AUPRC on the basis of 5,000 bootstrap samples generated from each models' predictions. The vertical dotted line represents the mean AUPRC computed from 5,000 bootstrap samples generated from a random prediction model. (B) Lift ratio (LR) curve for the ensemble-based prediction model, with gray lines representing the LR curves generated for 100 random prediction models. (C) Distribution of the area under the LR curve at 20% on the basis of random prediction models (gold), all challenge submissions teams (blue), the top-performing teams (gray points), and the postchallenge ensemble-based classifier (red).

arm across a range of risk prediction accuracies (Data Supplement). Results demonstrated that when patient selection considered the risk of early treatment discontinuation, fewer patients were required for the trial without a loss of statistical power. For example, if patient discontinuation was not considered, an average of 1,548 patients was needed to detect an HR of 1.30 at 80% statistical power and a false-positive rate of 5%; however, when selection into the trial was based on the ensemble-based model, the estimated sample size that was required for detecting an HR of 1.30 was reduced to 1,306 patients (Data Supplement).

DISCUSSION

A growing number of studies support the clinical value of prediction models for early treatment discontinuation on the basis of a patient's clinical characteristics.[34-37] Our results show that clinical

features can be used to identify patients with mCRPC who may respond adversely to docetaxel treatment. Previous prognostic models have focused on overall survival and identified important risk factors, including ALP, HB, albumin, PSA, lactate dehydrogenase, ECOG performance status, lesion site, and use of analgesics.[10,11] By using the results from the top seven teams in this study, we confirmed that these variables are predictive of poor prognosis and also discovered several predictive variables that are related to early discontinuation of docetaxel treatment, including PSA, RBC, calcium, AST, creatinine clearance, and total protein (Fig 4). Of interest, AST was used in many of the top-performing models and was found to be significantly elevated in the high-risk versus low-risk groups for discontinuation, which is concordant with previous observations in patients who were treated with first-line chemotherapeutics in

non–small-cell lung cancer.[37] Whereas additional investigations are needed to understand the clinical and biologic implications of risk factors in predicting docetaxel-related AEs, our results present the first findings, to our knowledge, focused on toxicity-induced treatment discontinuation as a result of docetaxel in the treatment of mCRPC.

Although the performance of the challenge and postchallenge models remained modest and lacked the accuracy needed for immediate clinical application,[38] this study is nevertheless a critical first step in the development of viable clinical tools. In particular, the challenge served to initiate the postchallenge community effort, which led to an ensemble-based prediction model that recorded performances greater than any individual model, demonstrating the power of collaborative communities as a paradigm for clinical informatics research.[39,40] The results presented here are the product of 34 independent, international teams that were focused on addressing a common, well-defined question within a short period of time.

Of importance, this challenge is the first to establish a performance benchmark for evaluating models that predict early failure of docetaxel treatment in patients with mCRPC, which will serve as a basis for developing future prediction models. Our results are encouraging and in line with a growing emphasis on the need for innovative approaches for clinical trial design.[41] Indeed, we demonstrated through a simulation study that identifying patients who discontinue treatment could reduce patient enrollment in clinical trials by significant numbers, especially when the desired effect size between controls and treatment is small.

We recognize that since the completion of the four trials used here, several promising therapies have emerged that have reshaped the treatment of mCRPC.[42] The predictive models were trained on AEs that resulted from docetaxel treatment and would need to be evaluated against additional trials and additional treatments to determine if they are generalizable. A second limitation of this study is that there were no restrictions imposed on the number of clinical features that were used to develop prediction models. We chose to impose few restrictions on the model developers with the goal of determining whether the provided baseline clinical features could be used in any manner to build predictive models of treatment discontinuation. As a result, the models that were submitted to the challenge were not necessarily optimized for clinical translatability, but focused on addressing the proposed question.

The DREAM Challenge described here exemplifies how open clinical trial data can be used to explore new questions and highlights the role of open challenges as a tool for the development and objective evaluation of clinical models. We also demonstrated the willingness of the research community to work together. It should be noted that the group of researchers who performed the postchallenge analysis, developed the ensemble predictor, and wrote this manuscript had never worked together before. The challenges we face in biomedical science are too great for siloed research to be the status quo moving forward. Fostering research in this manner is additional evidence that the biomedical research of tomorrow can and will be a team effort.

AUTHOR CONTRIBUTIONS

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