Deep transfer learning provides a *Pareto* improvement for multiethnic genomic prediction of diseases

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Abstract

Accurate predisposition assessment is essential for the prevention and early detection of diseases. Polygenic scores and machine learning models have been developed for disease prediction based on genetic variants and other risk factors. However, over 80% of genomic data were acquired from individuals of European descent. Other ethnic groups comprise the vast majority of the world population and have a severe data disadvantage. Due to the lack of suitable training data, clinico-genomic risk prediction is less accurate for the non-European population. Here we employ a transfer learning strategy to improve the clinico-genomic prediction of disease occurrence for data-disadvantaged populations. Our multiethnic machine learning experiments on real and synthetic datasets show that transfer learning can significantly improve disease prediction accuracy for data-disadvantaged populations. Under the transfer learning scheme, the prediction accuracy for the data-disadvantaged populations can be improved without compromising the prediction accuracy for other populations. Therefore, transfer learning provides a *Pareto* improvement toward equitable machine learning for genomic medicine.

Keywords: disease prediction, transfer learning, deep neural network, health equity

Introduction

Predicting disease occurrence based on clinico-genomic data is important to precision medicine. Traditionally, disease prediction was primarily based on epidemiological risk factors such as lifestyle variables and family history. The tremendous advances in high-throughput genotyping and genome sequencing technologies in recent years have enabled genome-wide association studies (GWAS) of large cohorts. The data and discoveries from GWAS provide a foundation for polygenic risk prediction for complex diseases. However, over 80% of the GWAS data were collected from people of European descent[1-5]. The genomic data paucity for other ethnic groups, which constitute the vast majority of the world's population, results in low-quality artificial intelligence (AI) models for the data-disadvantaged populations. The overall ethnic diversity in GWAS has not improved in recent years[1,6]. Genomic data inequality has become a new health hazard for the vast majority of the world's population and is generating new health disparities[7].

Polygenic scores have been extensively studied for disease risk assessment[8-15]. However, the polygenic scores are often inadequate for accurate disease prediction, which is partially due to: 1) complex diseases are caused not only by genetic factors but by a combination of genetic, environmental, and lifestyle factors; and 2) the linear polygenic models lack the expressive power and model capacity to capture the complex non-linear, non-additive interactions that are inherent in the genotype-phenotype relationship. It has been found that non-additive genetic interactions can significantly reduce the accuracy of polygenic prediction[16]. Recently, deep learning and other machine learning models have been developed to integrate genomic and epidemiological factors for disease prediction and prognosis[17-19]. In general, the deep learning models that excel at capturing complex non-linear interactions outperform conventional disease prediction models[20].

Polygenic scores derived from GWAS of predominantly European ancestry generalize poorly to other ancestry groups[6,21-25]. This challenge is being addressed on two fronts: data collection and computational method development. Large-scale efforts are underway to increase ethnic diversity in genomic research[26-28]. Recent studies also show that the polygenic prediction for non-European populations can be improved by calibrating parameters for genetic effect sizes or model sparsity (or shrinkage) patterns across ancestry groups in various regression models[29-33]. However, the linearity, additivity, distribution normality, and other assumptions made by these polygenic models (Bayesian or non-Bayesian) limit their capacity to learn and transfer complex representations across ancestry groups. Recently, we developed deep neural network (DNN) based transfer learning methods to reduce the disparity in multiethnic machine learning for cancer progression and survival prognosis from mRNA and protein expression data[7,34]. In this work, we test a deep transfer learning strategy for disease prediction from multiethnic GWAS data. We compare the performance of the transfer learning scheme to that of the current prevalent multiethnic machine learning schemes and find that transfer learning can significantly improve disease prediction for the data-disadvantaged ethnic groups.

Fairness-aware machine learning methods[35] generally rely on various build-in constraints or penalty terms in the loss function and training process to enforce performance parity across different subpopulations, resulting in a dilemmatic fairness-accuracy tradeoff[36,37]. The transfer learning scheme is not subject to such a tradeoff. The machine learning model trained for a data-abundant population can be utilized to aid in training the data-disadvantaged populations without reducing its prediction accuracy for the data-abundant population. Thus, transfer learning may provide a *Pareto* improvement[38], in which the prediction accuracy can be improved for the data-disadvantage populations while remaining unchanged for the data-abundant population (**Fig.1**).

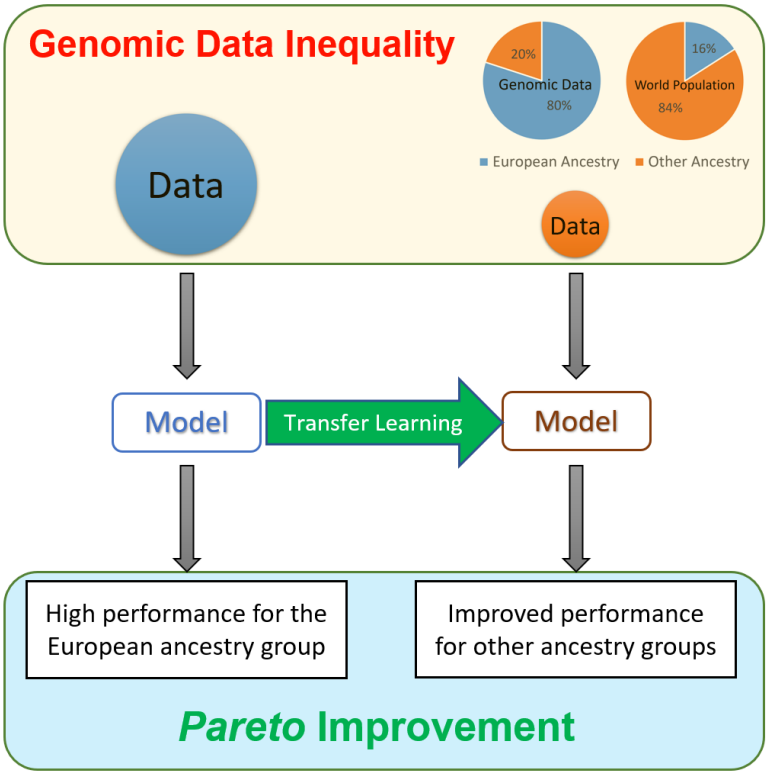

Fig. 1 Transfer learning provides a *Pareto* improvement toward more equitable machine learning for precision medicine. The conspicuous genomic data inequality confers a significant health risk to the data-disadvantaged populations. The transfer learning scheme can improve the AI model performance for the data-disadvantaged populations by consulting (but not affecting) the model for the data-rich population, thus leading to a *Pareto* improvement.

Results

Multiethnic machine learning schemes can be classified based on how they utilize the data from different subpopulations[7] (**Table 1**). Currently, the mixture and independent learning schemes are generally used for machine learning with multiethnic GWAS data. Mixture learning uses data from all ethnic groups indistinctly

for model training and testing. Independent learning trains and tests a model for each ethnic group separately. In our machine learning experiments, we find that both mixture and independent learning schemes generate models with low performance for the data-disadvantaged populations (DDPs). We also find that transfer learning can significantly improve machine learning model performance on the DDPs (**Table 1, Fig. 2**). In transfer learning, a model is first trained on the data of the European population (source domain), and then the knowledge learned is transferred to assist the model development for a DDP (target domain).

Multiethnic machine learning experiments on GWAS data

We compared the performance of the three multiethnic machine learning schemes using GWAS data. We assembled the datasets for our machine learning experiments using the data of two large multiethnic GWAS[39] from the OncoArray Consortium[40]. The input datasets for multiethnic machine learning experiments are summarized in **Table S1**.

The machine learning tasks are to predict the case/control status of lung cancer and prostate cancer from genotype and clinical data. For lung cancer, we used the top 500 SNPs, age, sex, and smoking status as the input variables. For prostate cancer, we used the top 1000 SNPs, age, and family history as the input variables. We used the mean AUROC[41] (Area under ROC Curve) from 20 independent runs of each machine learning experiment as the index to compare the machine learning model performance. The mixture learning scheme generated significant model performance gaps between the ethnic groups: 0.15 ($p = 2.45 \times 10^{-13}$) for lung cancer and 0.16 ($p = 1.39 \times 10^{-19}$) for prostate cancer. The independent learning scheme also generated significant model performance gaps: 0.16 ($p = 6.56 \times 10^{-15}$) for lung cancer and 0.13 ($p = 4.0 \times 10^{-10}$) for prostate cancer. These two schemes are widely used in multiethnic machine learning but are prone to generating machine learning models with low performance for data-disadvantaged populations (DDPs). Naïve transfer, in which the model trained using data from the source domain is applied directly to the target domain without adaptation, also generated models with low performance on the DDPs. The low performance of mixture learning for the DDPs (Mixture 2) and naïve transfer is consistent with previous observations of the low generalizability of polygenic scores developed using data of predominantly or exclusively European ancestry. In the transfer learning scheme, a model learned from the source domain with abundant training data (the European population) was used to improve machine learning in the target domain with insufficient training data (the DDPs). In our experiments, transfer learning improved the machine learning model performance on the DDPs by 16% for lung cancer and 20% for prostate cancer, compared with the average performance of mixture learning (mixture 2), independent learning (independent 2), and naïve transfer (**Table 1, Fig. 2**).

Table 1 Multiethnic machine learning schemes and experiments

Multiethnic Machine Learning Scheme	Experiment	Ethnic Composition		AUROC	
		Training Data	Testing Data	Lung Cancer	Prostate Cancer
Mixture Learning	Mixture 0	EUR + DDP	EUR + DDP	0.71	0.76
	Mixture 1		EUR	0.72	0.77
	Mixture 2		DDP	0.57	0.61
Independent Learning	Independent 1	EUR	EUR	0.70	0.78
	Independent 2	DDP	DDP	0.54	0.65
Naive Transfer	Naive Transfer	EUR	DDP	0.54	0.59
Transfer Learning	Transfer Learning	EUR (source domain) DDP (target domain)	DDP	0.64	0.74

AUROC: The mean of the Area under ROC Curve values from 20 independent runs for each experiment. **SD:** Synthetic data. **EUR**: European population. **DDP**: Data-disadvantaged population. For the machine learning experiments on lung cancer and prostate cancer data, Asian and African American populations are the data-disadvantaged population, respectively.

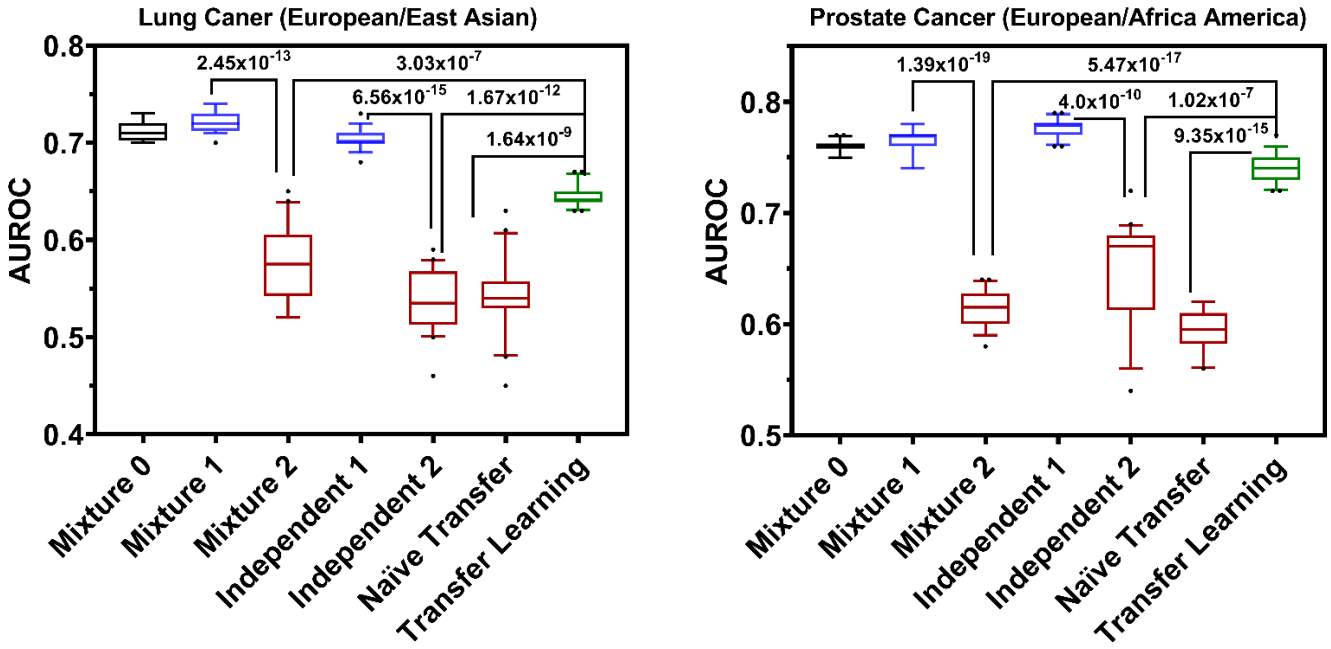

Fig. 2 Multiethnic machine learning scheme comparison. Machine learning experiments for predicting case/control status for (**A**) lung cancer and (**B**) prostate cancer GWAS participants using clinico-genomic data from GWAS. The assembled dataset for each cancer type contains two ethnic groups: European and East Asian for the lung cancer dataset and European and African American for the prostate cancer dataset. In each panel, the box plots show the AUROC values for the seven experiments (20 runs for each experiment). Box-plot elements are: center line, median; box limits, 25 and 75 percentiles; whiskers, 10–90 percentiles; points, outliers.

Multiethnic machine learning experiments on synthetic data

To compare the machine learning schemes, we conducted multiethnic experiments (as defined in Table 1) on the synthetic data for five ancestries. The five ancestry groups, African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS), represent the continental origins and global genetic diversity of human populations. We used the simulated genotype data of the five ancestry groups[31] downloaded from the Harvard Dataverse[42]. We assembled datasets to simulate the data inequality among ancestry groups. Each dataset contains genotype data of 10,000 individuals from the European ancestry group and 2,000 individuals from one of the four non-European ancestry groups. The allele frequency difference for 500 randomly selected causal SNPs between EUR and other populations is visualized using a heatmap (**Figure 3**). The heatmap shows the absolute minor allele frequency difference between the EUR population and the data-disadvantaged population populations AMR, SAS, EAS, and AFR. We constructed a statistical model to simulate the genotype-phenotype relationship (see the Method section) and generate the disease status (case/control) for the individuals. The synthetic data capture two typical characteristics of current multiethnic data: the data inequality and the data distribution discrepancy between ancestry groups, which are the key factors influencing the performance of different multiethnic machine learning schemes[7,34]. The disease heritability is also a parameter in the simulation model. We generated synthetic datasets using various combinations of the values of two parameters, h^2 and ρ, the heritability of the disease and the correlation of the genetic effect sizes between EUR and other populations (**Table 2** and **Table S1**). The case/control ratio for all the synthetic datasets is 1:1.

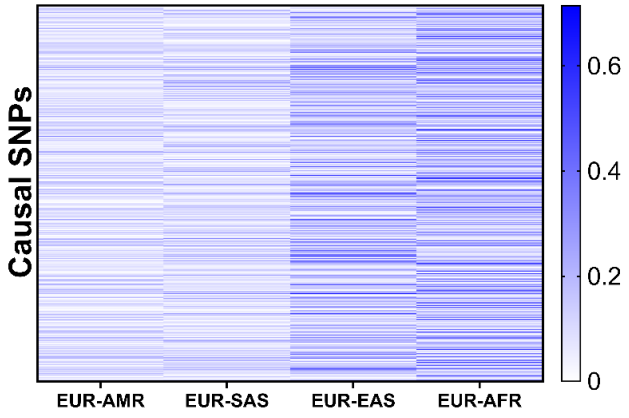

Fig. 3 Allele frequency difference between the EUR and each of the four data-disadvantaged populations. The heatmap shows the absolute difference in minor allele frequencies between the EUR population and the data-disadvantaged populations (DDPs), AMR, SAS, EAS, and AFR. Each row represents an SNP. The value of each cell $C_{ij} = |F_i^{EUR} - F_i^{DDP_j}|$, where F_i^{EUR} is the frequency of the minor allele of ith SNP in the EUR population, and $F_i^{DDP_j}$ is the frequency of the same allele in the jth DDP.

Table 2 Multiethnic machine learning experiments on synthetic data

Synthetic Datasets				AUROC						
ID	DDP	h^2	ρ	Mixture 0	Mixture 1	Mixture 2	Independent 1	Independent 2	Naive Transfer	Transfer Learning
SD1	AMR	0.50	0.80	0.74	0.75	0.70	0.76	0.62	0.62	0.72
SD2	SAS	0.50	0.77	0.72	0.73	0.69	0.74	0.62	0.61	0.71
SD3	EAS	0.50	0.58	0.73	0.74	0.67	0.72	0.64	0.62	0.69
SD4	AFR	0.50	0.54	0.72	0.73	0.65	0.73	0.66	0.57	0.68
SD5	AMR	0.25	0.80	0.61	0.62	0.59	0.62	0.55	0.55	0.60
SD6	SAS	0.25	0.77	0.58	0.59	0.57	0.61	0.56	0.56	0.60
SD7	EAS	0.25	0.58	0.57	0.58	0.55	0.60	0.56	0.57	0.59
SD8	AFR	0.25	0.54	0.60	0.60	0.57	0.60	0.56	0.54	0.58

AUROC: The mean Area under ROC Curve values from 20 independent runs for each experiment; **SD:** Synthetic data; **EUR**: European population; **DDP**: Data-disadvantaged population; **AFR**: African; **AMR**: Admixed American; **EAS**: East Asian; **SAS**: South Asian.

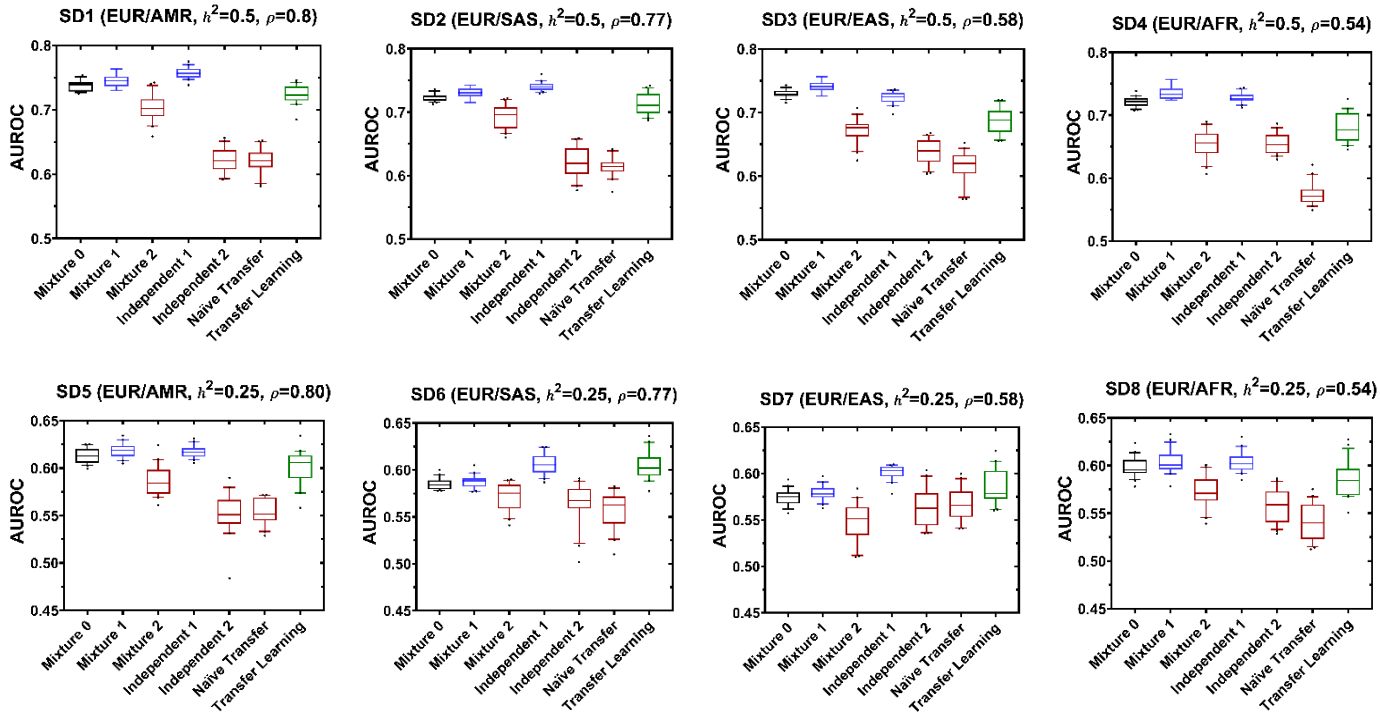

Fig. 4 Comparison of multiethnic machine learning schemes on synthetic data. In each panel, the box plots show the AUROC values for the seven experiments (20 runs for each experiment). Box-plot elements are center line, median; box limits, 25 and 75 percentiles; whiskers, 10–90 percentiles; points, outliers.

From the multiethnic machine learning experiments on all the real and synthetic datasets (**Table 1, Fig. 2; Table 2, Fig. 4;** and **Table S2, Fig. S1**), we observed a consistent performance pattern, which is defined by four prominent attributes: 1) Mixture learning generating model performance gap between the European population and the DDPs; 2) Independent learning generating model performance gap between the European population and the DDPs; 3) Low generalizability of model trained on EUR data to other ancestry groups indicated by the low performance of naïve transfer learning; and 4) Transfer learning outperforming mixture learning, independent learning and naive transfer on the DDPs. The results on synthetic data show that the performance pattern is consistent for different DDPs and simulation parameters (**Table 2, Fig. 4;** and **Table S2, Fig. S1**). As expected, the heritability (h^2) affects the prediction performance in all seven experiments. However, the performance pattern remains consistent at different levels of heritability ($h^2 = 0.5\ and\ h^2 = 0.25$). In the simulation model, the parameter ρ is the correlation of the genetic effect sizes and is set as a function of genetic distance between ancestry groups (see the Method section). Therefore, ρ represents the data distribution discrepancy between the EUR and DDPs. Our results show that the performance pattern is also robust against the variations of ρ. The overall performance comparison of the multiethnic machine learning schemes for the 14 synthetic datasets is shown in **Fig. S2**. For all the real and synthetic datasets, transfer learning provides the best performance on the DDPs.

Discussion

Precision medicine is becoming increasingly dependent on high-performance machine learning models. Large-scale clinico-genomic datasets are the foundation for the development of critical AI models for disease diagnostics, prognostics, and therapies. However, genomic data inequality is a severe impediment to equitable precision medicine, posing a significant health risk to the data-disadvantaged populations. Machine learning models based on data from primarily European ancestry must be tested for their validity, applicability, and accuracy in other ancestry groups.

This study shows that transfer learning can enhance disease prediction for data-disadvantaged populations, reducing the detrimental effects of genomic data inequality. The transfer learning scheme provides a Pareto improvement toward equitable machine learning for genomic medicine since it is not subject to the fairness-accuracy tradeoff, in contrast to the widely utilized constraint-based machine learning fairness approaches (**Fig.1**). In general, the *Pareto* improvement is desired because it creates a new situation in which certain parties in a system are better off without negatively affecting other parties in the system[38].

Methods

Data processing

The genotype, phenotype, and clinical data for lung cancer and prostate cancer datasets[43] were downloaded from dbGaP[44] (phs001273.v3.p2 and phs001391.v1.p1). Genetic ancestries of the GWAS participants calculated by GRAF-pop[45] were also downloaded from dbGaP. The selection of datasets was mainly based on the number of participants and the ethnic compositions. The selected datasets have more than 15,000 participants and over 2,000 participants from a non-European ancestry group.

We followed a standard quality-control process[46] using plink[47] (V1.9) to identify disease-associated single nucleotide polymorphism (SNPs) and remove outlier samples: 1) We eliminated SNPs with a missing rate larger than 20% and then filtered samples with a missing SNP rate higher than 20% and filtered samples with sex discrepancy; 2) We removed genetic marker SNPs with minor allele frequency (MAF) lower than 0.05 to reduce the size of feature set; 3) We removed the SNPs with a Hardy-Weinberg Equilibrium (HWE) p-value less than 10^{-5}; 4) To eliminate data redundancy from Linkage Disequilibrium (LD), we used a sliding window of 50 SNPs and set the step length to 5 SNPs and set the LD cut-off coefficient to 0.2. The resulting datasets for our machine learning experiments are summarized in **Table 1**.

We split each dataset into three parts: training set, validation set, and testing set, with 80%, 10%, and 10% of the cases, respectively, stratified by ancestry and class label (case/control). We randomly split the validation set and testing set with 20 different random seeds. The ancestry and case/control proportions were kept the same for all three sets in each partition. The association analysis for the training set was conducted using the additive logistic regression model from the Plink software. We used a p-value threshold ($p<10^{-3}$) to select the top SNPs. The ANOVA F-value for each SNP was calculated for the training samples to select the input features for machine learning. We selected the top 500 SNPs for Lung cancer and 1000 SNPs for Prostate cancer. The feature mask, ANOVA F-value, and p values were calculated using the *SelectKBest* function in the *sklearn* package.

Data simulation

We used a statistical model to generate synthetic datasets. Each synthetic dataset *D* is a combination of two subsets, $D = D_1 \cup D_2$, $D_1 = \{x_{ij}, y_i\}_{i=1}^{m}$, $D_2 = \{x'_{ij}, y'_i\}_{i=1}^{n}$, where D_1 represents the European group, D_2 represents the DDP group, m and n are the numbers of samples in the two groups, x_{ij} is the jth feature of sample i in the European group, x'_{ij} is the jth feature of sample i in the DDP group, y_i is the case/control label of sample i in the European group, y'_i is the case/control label of sample i in the DDP group. The feature

matrix x_{ij} and x'_{ij} were sampled from the multi-ancestral genotype dataset, which contains simulated whole-genome genotype data for 120,000 individuals of each of the five ancestries, African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS). We applied a quality-control process for each ancestry group to remove the SNPs with MAF<0.05 or HWE p-value < 10^{-4}. We randomly selected 500 SNPs as the causal SNPs, 10,000 EUR individuals, and 2,000 individuals from each of the four non-EUR populations. We assembled four datasets, and each contains the genotype data of the selected causal SNPs for the 10,000 EUR individuals and 2,000 individuals of one of the non-EUR populations. The label of the ith EUR individual is generated using the function $y_i = \begin{cases} 1 & if\ g_i > thr \\ 0 & otherwise \end{cases}$, where $g_i = h\sum_{j=1}^{500} w_j * x_{ij} + \sqrt{1-h^2} * \zeta$, thr is the median value of $\{g_i\}$, w_j is the effect size of the jth SNP, ζ is sampled from a standard normal distribution with a truncated domain [-1,1], and h^2 represents heritability. Similarly, The label of the ith non-EUR individual is generated using function $y'_i = \begin{cases} 1 & if\ g_i > thr \\ 0 & otherwise \end{cases}$, $g'_i = h\sum_{j=1}^{500} w'_j * x'_{ij} + \sqrt{1-h^2} * \zeta$, where thr' is the median value of $\{g'_i\}$, w'_j is the effect size of the jth SNP. The SNP genetic effect vector for the European group $W = [w_1, w_2, w_3, \ldots w_n]$ was generated from a random sampling of the uniform distribution over $[0,1)$. $W' = [w'_1, w'_2, w'_3, \ldots w'_n]$ is generated using the following equation: $W' = \rho * W + \sqrt{1-\rho^2} * \zeta$, where ρ is the correlation of the genetic effect sizes between EUR and the DDP, ζ is sampled from a standard normal distribution with a truncated domain [-1,1]. We ensembled synthetic datasets that contains data from EUR and one of the four DDPs: {EUR, AFR}, {EUR, AMR}, {EUR, EAS}, {EUR, SAS}. We used 14 different combinations of the values of h^2 and ρ to generate the synthetic datasets (**Table 2** and **Table S2**). We generated synthetic data at the two different levels of heritability ($h^2 = 0.5\ and\ h^2$=0.25). The parameter ρ is a function of the genetic distance between the populations. The genetic distance between EUR and the jth DDP is $d_j = \sum_{i=1}^{500} |F_i^{EUR} - F_i^{DDP_j}|$, where F_i^{EUR} is the frequency of the minor allele of ith causal SNP in the EUR population, and $F_i^{DDP_j}$ is the frequency of the same allele in the jth DDP. The genetic distances are $d_0 = 42.7$ (EUR - AMR), $d_1 = 46.1$ (EUR - SAS), $d_2 = 80.6$ (EUR - EAS), $d_3 = 94.1$ (EUR - AFR). We used the function $\rho_j = \rho_0 \left(\frac{d_0}{d_j}\right)^r$ to generate values for parameter ρ, where $\rho_0 = 0.8$. We set $r = 0.5$ to generate the ρ values for synthetic datasets 1-8 (**Table 2**) and set $r = 1.0$ to generate the ρ values for synthetic datasets 9-16 (**Table S2**, SD9 and SD13 are the same as SD1 and SD5).

Deep transfer learning

We used the Keras (https://keras.io/), and Tensorflow (https://www.tensorflow.org/) packages to build the deep neural network (DNN) models. We used a pyramid architecture[48] with four layers: an input layer with K

nodes for the input features of genotype and other risk factors, where the input feature number K=503 for the lung cancer dataset, including 500 SNPs, age, sex, and smoking status, K=1002 for the prostate cancer dataset, including 1,000 SNPs, age, and family history, and K=500 for the synthetic datasets (500 SNPs); two hidden layers including a fully connected layer with 100 nodes followed by a dropout layer[49]; and a logistic regression output layer. We used the stochastic gradient descent (SGD) algorithm with a learning rate of 0.25 to minimize a loss function consisting of a binary cross-entropy term and two regularization terms: $l(W) = -\sum_{i=1}^{m}(y_i\, log(\hat{y}_i) + (1 - y_i)\log(1 - \hat{y}_i)) + \lambda_1|W| + \lambda_2\|W\|_2$, where y_i is the observed control/case label for individual i, $\hat{y}_i$ is the predicted label for individual i, and W represents the weights in the DNN. We applied the ReLU activation function $f(x) = max(0, x)$ to the output of the hidden layer to avoid the gradient vanish problem. For each drop out layer, we set the dropout probability $p = 0.5$ to randomly omit half of the weights during the training to reduce the collinearity between feature detectors. We split the data into multiple mini-batches (batch size = 32) for training to speed up the computation and improve the model prediction performance. We set the maximum number of iterations at 200 and applied the Nesterov momemtum[50] method (with momentum=0.9 for each DNN model) to avoid premature stopping. We set the learning rate decay factor at 0.003 to avoid non-convergence during training. We also used early stopping with a patience value of 200 iterations to monitor the validation accuracy during model fitting. The two regularization terms λ_1 and λ_2 were set at 0.001.

In the transfer learning scheme, knowledge learned from the source domain, where training data is abundant, is transferred to assist the learning task for the target domain, where training data is inadequate[51-58]. The transferred knowledge is not the explicit knowledge expressed using mathematical or natural languages but is encoded in the machine learning model, for example, the structure and parameters of a neural network. We used the European ancestry population as the source domain and a DDP as the target domain. We adopted a supervised fine-tuning algorithm for transfer learning. We first pretrained a DNN model using the source domain data: $M \sim f(Y_{Source}|X_{Source})$, wehre Y_{Source} is the class label of each individual of the European group, X_{Source} is the input feature data of the European group. We trained the model using the parameters described above. After the pretraining, we fine-tuned the DNN model with the backpropagation method using the target domain data: $M' = fine_tuning(M \mid Y_{Target}, X_{Target})$, where M' is the final model. In the fine-tuning, the learning rate was set at 0.25, and the batch size was set at 32, as the model has been partially fitted and the target domain dataset is smaller.

Machine learning model performance evaluation and comparison

We performed 20 runs for each experiment. Each run uses the same training set but a different random splitting of validation and testing sets. We used the Area Under ROC Curve[41] (AUROC) to evaluate machine

learning model performance. We used the one-sided paired t-test to calculate the p-values for the statistical significance assessment in the machine learning model performance comparisons (**Fig. 2** and **Fig. S2**).

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Supplementary information

Table S1 The datasets used for machine learning experiments

Lung Cancer			Prostate Cancer		
European	Case	9675	European	Case	28385
	Control	8107		Control	19829
East Asian	Case	1363	African American	Case	1418
	Control	801		Control	2021

Table S2 Multiethnic machine learning experiments on synthetic data

Synthetic Datasets				AUROC						
ID	DDP	h^2	ρ	Mixture 0	Mixture 1	Mixture 2	Independent 1	Independent 2	Naive Transfer	Transfer Learning
SD9*	AMR	0.50	0.80	0.74	0.75	0.70	0.76	0.62	0.62	0.72
SD10	SAS	0.50	0.74	0.72	0.72	0.70	0.73	0.64	0.61	0.72
SD11	EAS	0.50	0.42	0.66	0.67	0.59	0.72	0.63	0.59	0.66
SD12	AFR	0.50	0.36	0.65	0.68	0.53	0.73	0.63	0.55	0.66
SD13*	AMR	0.25	0.80	0.61	0.62	0.59	0.62	0.55	0.55	0.60
SD14	SAS	0.25	0.74	0.58	0.59	0.57	0.60	0.57	0.55	0.62
SD15	EAS	0.25	0.42	0.58	0.59	0.54	0.61	0.55	0.55	0.57
SD16	AFR	0.25	0.36	0.60	0.60	0.57	0.61	0.57	0.53	0.58

AUROC: The mean Area under ROC Curve values from 20 independent runs for each experiment; **SD:** Synthetic data; **EUR**: European population; **DDP**: Data-disadvantaged population; **AFR**: African; **AMR**: Admixed American; **EAS**: East Asian; **SAS**: South Asian. *SD9 and SD13 are the same as SD1 and SD5 and are included here for comparison.

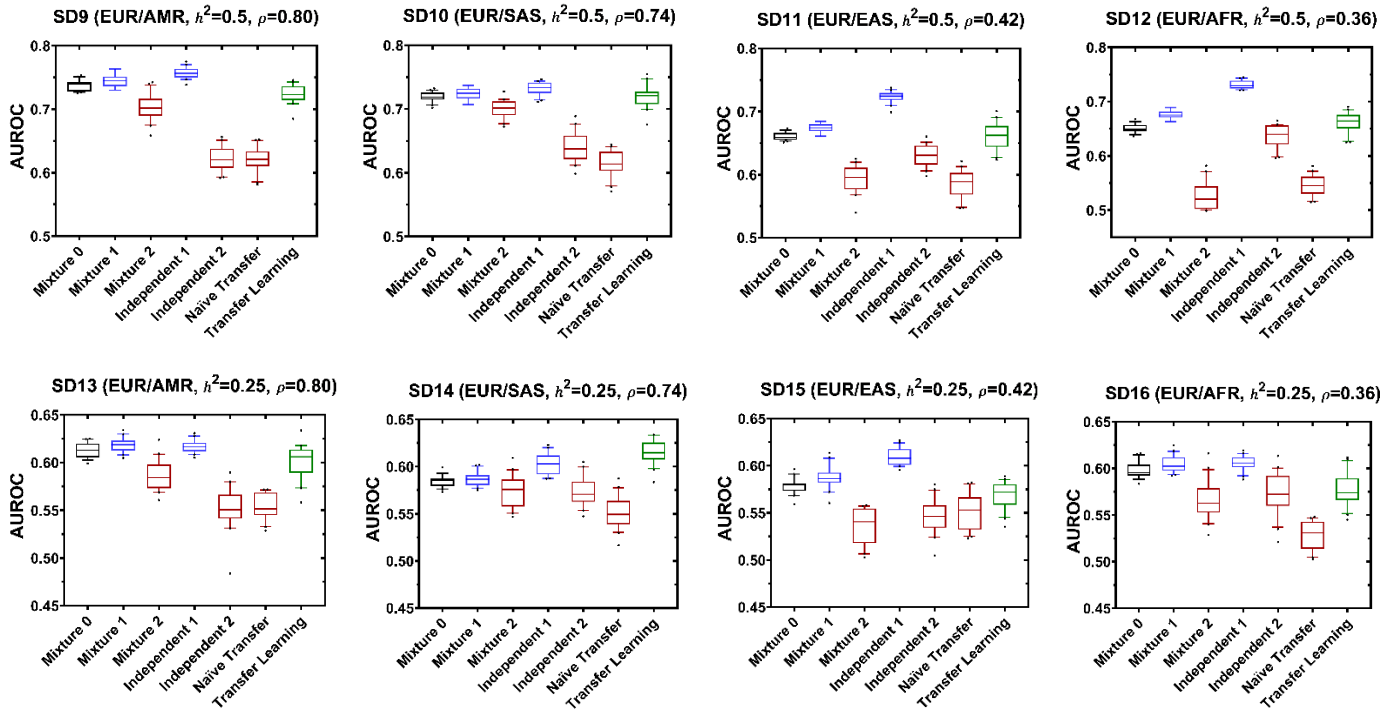

Fig. S1 Comparison of multiethnic machine learning schemes on synthetic data. In each panel, the box plots show the AUROC values for the seven experiments (20 runs for each experiment). Box-plot elements are center line, median; box limits, 25 and 75 percentiles; whiskers, 10–90 percentiles; points, outliers. SD9 and SD13 are the same as SD1 and SD5 and are included here for comparison.

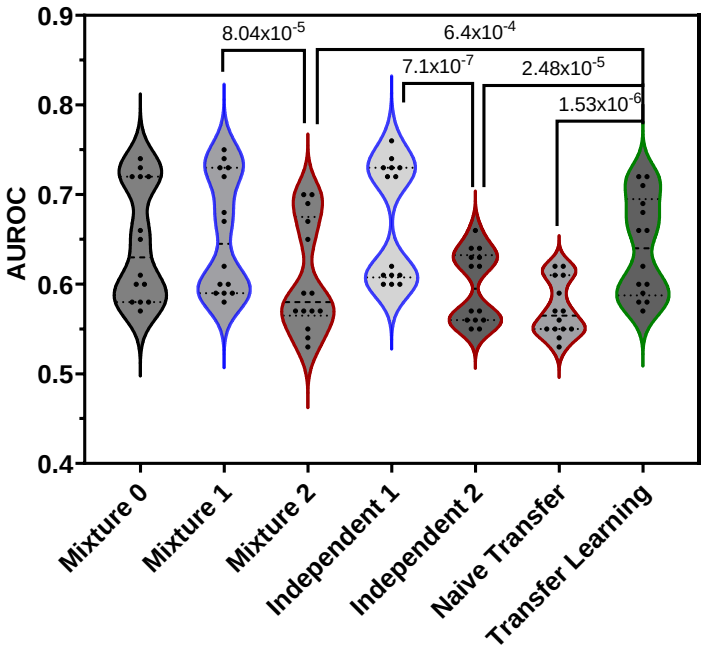

Fig. S2 Comparison of multiethnic machine learning schemes on the 14 synthetic datasets. Each violin plot shows the AUROC (area under the ROC curve) values for a machine learning experiment defined in Table 1. Each dot represents the mean AUROC of 20 runs, as shown in Table 2 and Table S1.