

# Algorithm Fairness in AI for Medicine and Healthcare

Richard J. Chen<sup>1,2,3,4</sup>, Tiffany Y. Chen<sup>1,3</sup>, Jana Lipkova<sup>1,2,3</sup>, Judy J. Wang<sup>1,5</sup>, Drew F.K. Williamson<sup>1,3</sup>, Ming Y. Lu<sup>1,3,4</sup>, Sharifa Sahai<sup>1,2,3</sup>, and Faisal Mahmood<sup>\*1,3,4</sup>

<sup>1</sup>*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

<sup>2</sup>*Department of Biomedical Informatics, Harvard Medical School, Boston, MA*

<sup>3</sup>*Cancer Program, Broad Institute of Harvard and MIT, Cambridge, MA*

<sup>4</sup>*Cancer Data Science Program, Dana-Farber Cancer Institute, Boston, MA*

<sup>5</sup>*Boston University School of Medicine, Boston, MA*

**\*Correspondence:**

Faisal Mahmood

60 Fenwood Road, Hale Building for Transformative Medicine

Brigham and Women's Hospital, Harvard Medical School

Boston, MA 02445

faisalmahmood@bwh.harvard.edu

## Abstract

**In the current development and deployment of many artificial intelligence (AI) systems in health-care, algorithm fairness is a challenging problem in delivering equitable care. Recent evaluation of AI models stratified across race sub-populations have revealed enormous inequalities in how patients are diagnosed, given treatments, and billed for healthcare costs. In this perspective article, we summarize the intersectional field of fairness in machine learning through the context of current issues in health-care, outline how algorithmic biases (*e.g.* - image acquisition, genetic variation, intra-observer labeling variability) arise in current clinical workflows and their resulting healthcare disparities. Lastly, we also review emerging strategies for mitigating bias via decentralized learning, disentanglement, and model explainability.**

## Introduction

Healthcare disparities continue to exist in medicine as a reflection of historical and current socioeconomic inequities, as well as group biases from the perpetuation of cultural stereotypes<sup>1–4</sup>. Though traditionally viewed through the lens of race and ethnicity, healthcare disparities encompass a wide range of dimensions, including, but not limited to: socioeconomic status, insurance status, education status, language, age, gender, sexual identity/orientation, and body mass index (BMI)<sup>5–8</sup>. These disparities often encompass all 5 domains of the social determinants of health as defined by the US Department of Health and Human Services (economic stability, education access and quality, healthcare access and quality, neighborhood and built environment, and social and community context), which were first established to begin disentangling causal factors for worsening health outcomes and mistrust in the healthcare system<sup>1,9–11</sup>. Historically, healthcare disparities began to become more widely recognized in the early 2000s with Surgeon General's reports documenting the disparities in tobacco use and access to mental health care by different racial and ethnic groups<sup>12</sup>. Another example can be seen in maternal morbidity, in which trends in pregnancy-related mortality in the US when stratified by race/ethnicity showed significantly higher pregnancy-related deaths amongst non-Hispanic black women due to disparate healthcare access and poor economic stability<sup>13,14</sup>. The most recent example is seen in the calculation of estimated glomerular filtration rate (eGFR) as a clinical biomarker and diagnostic tool for chronic kidney disease (CKD)<sup>15–17</sup>. Historically, race, specifically if the patient was African American, has been used as a parameter when calculating eGFR. However, this has led to overestimation of eGFR in black Americans and thus, potential under-diagnosis of CKD, which can greatly affect the clinical care (treatment plan, specialist referrals, clinical trial eligibility, renal transplant wait-list time) of black patients<sup>18–20</sup>. Understanding the

sources of these disparities would guide public policy on not only developing new clinical criteria for early detection of under-served patients, but also regulating the current development of machine learning algorithms trained with biased data constructed from historical inequities.

With the recent proliferation of AI algorithms in clinical deployment, there is a large ethical concern about the disparate impact these models will have at deployment time, especially on ethnic minority subpopulations and other underrepresented communities<sup>21-28</sup>. Recent audit studies have shown that AI algorithms may discover spurious causal structure in the data that correlate with protected identity status, leading to: 1) privacy leakage of race / ethnicity, and 2) misdiagnoses in using ethnicity as a shortcut for predicting outcome<sup>23,29,30</sup>. For instance, on pathology images, recent work has shown that H&E stain intensity is able to predict ethnicity on The Cancer Genome Atlas (TCGA) due to site-specific stain protocols and region-specific demography data. On radiology images, Convolutional Neural Networks (CNNs) will routinely under-diagnosis Hispanic and Black patients at a disproportionate rate due to insurance type and potential lack of access to healthcare<sup>30</sup>. Despite these large disparities in performance, there is a lack of public policy on regulating AI algorithms in U.S. Federal Food and Drug Administration (FDA) approval pathways to train and evaluate on diverse protected subgroups such as self-reported race and ethnicity. With 70 algorithms to date having received approval from the FDA as AI-based software as a medical devices (AI-SaMDs), AI is poised to automate many clinical paradigms that involve subjective human interpretation for disease diagnosis, prognosis, and treatment over the next decade, and if left unchecked will amplify many existing healthcare inequalities that already impact under-served subpopulations<sup>31,32</sup>.

In this Perspective, we build on previous work by examining current challenges in algorithm fairness from the perspective of medical dataset shift in AI-SaMD deployment. Though health disparities and algorithm fairness are both well-reviewed areas, much of the health fairness discussion has been focused on the choice of data inductive biases such as race-specific covariates in simple risk calculators, and overlooks the broader challenges in developing fault-tolerant AI algorithms in medicine<sup>18,19</sup>. Moreover, while current statistical frameworks for fairness aim at learning invariance to protected class identity, such models ignore causal structure between latent biological factors such as ancestry and their associated diseases across ethnic subpopulations<sup>25</sup>. Our Perspective begins by first providing a succinct overview of current evaluation metrics and bias mitigation strategies for fairness, followed by a discussion on how genetic variation, differences in image acquisition techniques, and evolving population shifts will become obstacles in evaluation of AI-SaMDs at deployment time. Lastly, we highlight an emerging technology known as federated learning which can train decentralized machine learning algorithms across multiple institutions with privacy-preserving guarantees, and

its relevant intersection with fairness and its role in AI-SaMD deployment.

### **Box 1. Glossary of Terms.**

**Health Disparities:** Group-level inequalities as a result of socioeconomic factors and social determinants of health, such as: insurance status, education level, average income in Zipcode, language, age, gender, sexual identity / orientation, BMI

**(Self-Reported) Race:** A recently-evolved human construct in categorizing human populations, over-loading taxonomies such as ancestry, ethnicity, and nationality.

**Protected / Sensitive Attributes:** Patient-level metadata that we would like our algorithm to be non-discriminatory against in predicting outcomes.

**Disparate Treatment:** Intentional discrimination of protected subgroups. Disparate treatment is also a feature in machine learning algorithms that include sensitive attribute information as direct input, or have confounding features that explain the sensitive attribute.

**Disparate Impact:** Unintentional discrimination as a result of disproportionate impact on protected subgroups.

**Model Auditing:** Post-hoc assessment of algorithm biases via interpretability.

**AI-SaMD:** Artificial Intelligence-based Software as a Medical Devices, a categorization of medical devices undergoing regulation by the U.S. Food and Drug Administration (FDA).

**Dataset Shift:** Mismatch in train (source) and test (target) dataset distributions.

**Domain Adaptation:** Techniques that correct for dataset shift in the source and target distribution. Domain adaptation methods typically match the input spaces of the source and target distribution via techniques such as importance weighting, or in the feature space via adversarial learning.

**Adversarial Learning:** Modification of learning objective in deep learning classifiers to learn sensitive attribute-invariant intermediate feature representations.

**Federated Learning:** A form of distributed learning that trains neural networks on local clients and send update weight parameters to a centralized server, without sharing data.

**Disentanglement:** A property of intermediate feature representations from deep neural networks, in which individual features control independent sources of variation in the data.

## **Fairness and Machine Learning**

Current statistical frameworks for fair machine learning aim at learning neutral models that are: 1) invariant to protected class identities when predicting outcomes, and 2) have non-discriminatory impact on protected

subgroups with equalized outcomes<sup>33</sup>. Formally, for a given sample with features  $X$  with target label  $Y$ , let  $A$  be a protected attribute that denotes a sensitive characteristic about the population of sample  $X$  that we want our model to be non-discriminatory against during evaluation in predicting  $Y$ . In legal history, fairness first emerged as a research problem in developing non-discrimination laws such as the 1964 United States (U.S.) Civil Rights Act, which has made it illegal to discriminate based on legally-protected protected classes (e.g. - race, color, sex, national origin) in Federal programs (Title VI) and employment (Title VII). In developing and evaluating non-discrimination in algorithms, many explored notions of fairness have been inspired by two doctrines in current discrimination law on mitigating: 1) disparate treatment, which is intentional discrimination by protected subgroups (e.g. - using protected attributes for decision-making), followed by 2) disparate impact, in which decisions have a disproportionate impact on protected subgroups<sup>34</sup>.

To mitigate disparate treatment in algorithms, the most intuitive and simple approach is fairness through unawareness, in which protected attributes are removed as direct inputs into algorithms, as recommended in current discussions on race-specific covariates in risk calculators<sup>17</sup>. However, denying protected attribute information has been shown to be insufficient in non-discrimination and satisfying fairness guarantees for many applications, as other input features may be unknown confounders that correlate with protected group membership<sup>35,36</sup>. For instance, a canonical example of disparate impact is the 1998 criminal risk assessment tool Correctional Offender Management Profiling for Alternative Sanctions (COMPAS) which predicts recidivism (e.g. - committing a misdemeanor or felony, on a scale from 1-10) within 2 years after reassessment. In contrast with risk calculators developed in healthcare, COMPAS excludes race as a covariate in predicting recidivism, which was contended as fair as risk scores should have equal meaning despite defendant's race. For instance, amongst defendants assigned a COMPAS score of 7, 60% and 61% of white and black defendants reoffended respectively. However, in 2016, news organization ProPublica argued that this notion of fairness was unfairly biased towards black defendants<sup>37</sup>. Despite COMPAS being blind to race, of defendants who did not reoffend, blacks were approximately twice-as-likely to be assigned medium-to-high risk scores (44%) as whites (22%), which creates a outcome disparity in which blacks are ultimately given harsher treatments. Also at the heart of this example is an accuracy-fairness tradeoff in which differing notions of disparate impact are in conflict with one another, which has since motivated the ongoing development of formal definitions of group fairness evaluation criteria in supervised learning algorithms, as shown in **Box 1**<sup>38,39</sup>. For instance, whereas fairness via Predictive Quality Parity (or Calibration) was satisfied in demonstrating equal risk scores for white and black defendants who re-offended, Equalized Odds was violated due to unequal False Positive Rates (FPRs).

To satisfy these two notions of fairness, many techniques have been developed that adapt existing algorithms with: 1) pre-processing steps that remove, augment, or reweight the input space to eliminate confounding bias<sup>40–44</sup>, 2) in-processing steps that construct additional optimization constraint or regularization loss functions that penalize non-discrimination<sup>45–48</sup>, and 3) post-processing steps that apply correction to calibrate model predictions across subgroups<sup>33,38,49,50</sup>. We briefly review several below with some noticeable examples that have been applied to many biomedical datasets shown in **Table 1**:

## Preprocessing

Algorithmic biases in healthcare stem from historical inequities that create spurious associations would link protected class identity to disease outcome in the dataset, when the true underlying causal factor stems from poor social determinants of health. In training algorithms that on health data that have internalized such biases, the distribution of outcomes across ethnicity may be skewed in which under-served Hispanic and Black patients have more delayed referrals for cancer screening, which may result in more high-grade, invasive phenotypes at the time of radiology imaging or tumor biopsy. Such sources of labeling prejudice are known as negative legacy, or sample selection bias, in which biased data curation protocols may induce correlations between protected attributes and other features, and may result in failed convergence of the training algorithm<sup>45</sup>. As a result, many data preprocessing steps have been developed beyond "fairness through unawareness", such as importance weighting, resampling, data transformation, and variable blinding that would correct for confounding features and data curation protocols.

*Importance Weighting:* Importance weighting first emerged as an approach for eliminating covariate shift, e.g. -  $P_{\text{train}}(X) \neq P_{\text{test}}(X)$ , in which the train distribution is reweighted to match the test distribution via computing a density ratio  $\frac{P_{\text{train}}(X)}{P_{\text{test}}(X)}$ <sup>78,79</sup>. In fairness, importance weighting is used to reweight infrequent samples belonging to protected subgroups followed by optimization of fairness metrics such as TPR and FPR for that subgroups<sup>40–44</sup>. For clinical tasks in which the distributions for demography or disease prevalence may not match in the train and test population, importance weighting has been extensively used to correct for sample selection bias. For instance, In MRI scans, importance weighting has been previously applied to reweigh instances of sparsely annotated voxels in Alzheimer's disease diagnosis<sup>80,81</sup>. In skin lesion classification, reweighting approaches have similarly been used for learning with noisy labels<sup>82</sup>. A noticeable limitation is that classifiers trained with reweighted samples may not have robust performance on multiple domains, as well as can induce high variance in the estimator for severely underrepresented subgroups<sup>83,84</sup>.

Dataset	Modalities	Num. Patients	Female	W	B	A	HL	PH	IA	O	Audit
MSK-IMPACT <sup>51</sup>	Genomics	10336	0.502	-	-	-	-	-	-	-	N/A
TCGA <sup>52</sup>	Pathology, MRI/CT, Genomics	10953	0.485	0.675	0.079	0.059	0.003	0.001	0.002	-	29
UK Biobank <sup>53</sup>	Genomics	503317	0.544	0.946	0.016	0.023	-	-	-	0.015	54
PIONEER <sup>55</sup>	Genomics	1482	0.434	-	-	1.000	-	-	-	-	N/A
eMerge Network <sup>56,57</sup>	Genomics	20247	-	0.777	0.161	0.001	-	0.002	0.002	0.045	58
NHANES <sup>59</sup> (2017-2018)	Lab Measurements	15560	0.504	0.339	0.263	0.105	0.227	-	-	0.065	17
Undisclosed EMR Data <sup>22</sup>	EMRs, Billing Transactions	49618	0.629	0.877	0.123	-	-	-	-	-	22
OAI <sup>60</sup>	Limb XR	4172	0.574	0.709	0.291	-	-	-	-	-	23, 61
SIIM-ISIC <sup>62</sup>	Dermoscopy	2056	0.480	-	-	-	-	-	-	-	63, 64
NIH AREDS <sup>65</sup>	Fundus Photography	4203	0.567	0.977	0.014	0.080	0.020	0.012	0.010	-	66
RadFusion <sup>67</sup>	EMRs, CT	1794	0.521	0.626	-	-	-	-	-	0.374	67
CPTAC <sup>68</sup>	Pathology, Proteomics	2347	0.395	0.365	0.032	0.100	0.023	0.001	0.004	0.491	N/A
MIMIC <sup>69,69</sup>	Chest XR, EMRs, Waveforms	43,005	0.441	0.682	0.092	0.029	0.04	0.002	0.002	-	30, 70-72
CheXpert <sup>73</sup>	Chest XR	64,740	0.410	0.670	0.060	0.130	-	-	-	0.113	30, 71
NIH NLST <sup>74</sup>	Chest XR, Spiral CT	53456	0.410	0.908	0.044	0.020	0.017	0.004	0.004	0.020	71, 75
RSPECT <sup>76</sup>	CT	270	0.530	0.900	0.100	-	-	-	-	-	71
DHA <sup>77</sup>	Limb XR	691	0.492	0.520	0.482	-	-	-	-	-	71

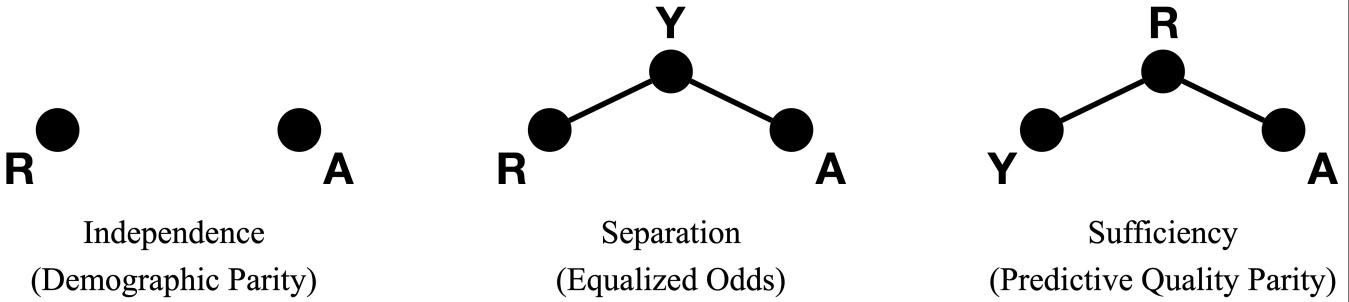
**Table 1. Demography of popular biomedical datasets used in machine learning and fairness.** Reported demography data were obtained for all patient populations in the original dataset, though model auditing may use only certain subsets due to missing labels and/or insufficient samples for evaluation in extremely under-represented minorities. Abbreviations: W = White, B = Black, A = Asian, HL = Hispanic / Latino, PH = Pacific Islander / Native Hawaiian, IA = American Indian / Alaskan Native. O = Unknown or Other. “-” denote demographic data not made publicly-available or acquired.

*Targeted Data Collection and Resampling:* In practice, many empirical and real-world studies have found that increasing the size of the dataset is able to mitigate biases<sup>85</sup>. Though audits of current publicly-available and commercial AI algorithms have revealed large performance disparities, collecting data for the under-represented subgroup is able to reduce performance gaps<sup>86,87</sup>. However, such targeted data collection may pose ethical and privacy concerns as a result of additional surveillance, as well as practical limitations especially in collecting protected health information due to stringent data interoperability standards<sup>88</sup>. Similar to importance weighting, resampling aims to correct for sample selection bias via obtaining more fair subsamples of the original training dataset, and can be intuitively applied to correct for under-representation of subgroups<sup>86,89–92</sup>. However, a computational challenge in fair resampling is maintaining feature diversity, in which over-sampling to correct for under-representation may instead decrease feature diversity. As a result, the development of frameworks for understanding data subsampling has emerged as its own subfield tangent to fair machine learning. One such framework is determinantal point process ( $k$ -DPP), which proposes quantifiable measures for combinatorial subgroup diversity (via Shannon Entropy) and geometric feature diversity (via measuring the volume of the  $k$ -dimensional feature space)<sup>93</sup>. In tandem with resampling is the problem of optimal data (or resource) allocation in operationalizing dataset collection in statistical surveys, as well as game-theoretic frameworks for understanding the influence of individual data points via Shapley values, which may refine resampling techniques to developing fair and diverse training datasets<sup>94–97</sup>. For instance, group distributionally robust optimization (GDRO) is a technique developed to minimize the maximum empirical risk over subgroups with respect to fairness definitions such as disparate impact and mistreatment minimization, and has recently been shown to adapt well to medical imaging tasks such as skin lesion classification<sup>88,98,99</sup>. Though data allocation would not fix datasets with labeling prejudice, allocations could be used to audit the training set used to develop algorithms for biases.

## In-processing

In addition to eliminating disparate impact of algorithms from the input space, the bulk of many approaches adopt a regularization or adversarial loss term within the model that penalize learning discriminatory features in  $X$  in predicting outcomes. For example, in structured data modalities such as imaging, many medical imaging modalities such as radiology, pathology, and even fundus photography images have been showed to leak and detect age, gender, and race from subtle cues in the input space<sup>29,100,101</sup>. These methods can be separated into two classes: 1) constraint optimization approaches that directly impose a non-discrimination term on the learning objective of a probabilistic discriminative model, and 2) fair representation methods, which are generally deep learning-based and can be unsupervised unsupervised in learning invariance to  $A$ .

**Box 2. Brief background on fairness criteria.**



For binary classification tasks,  $Y \in \{0, 1\}$  denotes a binary target label used to supervise our model, with  $R \in [0, 1]$  denoting the classification score  $P(Y|X)$  made by our model. For clinical tasks,  $Y$  can refer to objective health outcomes (*e.g.* survival, response-to-treatment), or subjective clinical annotations and diagnoses (*e.g.* stage, grade, or subtype of disease). In evaluating models for non-discrimination, three representative fairness metrics are used in current practice: a) Demographic Parity, b) Equalized Odds, and c) Calibration. In satisfying these fairness criterias, not all criterion can be satisfied at the same time.

*a. Demographic Parity.* Demographic Parity asserts that the fraction of positive predictions made the model should be equal across protected subgroups, satisfying the **independence** criteria  $R \perp A$  via the constraint:

$$\mathbb{P}\{R = 1 | A = a\} = \mathbb{P}\{R = 1 | A = b\} \quad (1)$$

for different subgroups  $a, b$ . Independence reflects the notion that decisions should be made independently of the subgroup identity. However, note that demographic parity only constrains the rate of positive predictions, and does not consider the rate at which the ground truth label may actually occurs in the subgroups. For instance, for  $Y = 1$  indicating kidney failure, disparate access to healthcare may self-select black patients at a relatively greater proportion than whites in the population, however, equalizing model predictions may decrease the number of black patients that are positively predicted.

*b. Equalized Odds.* Equalized Odds asserts that the true positive and false positive rates (TPR, FPR) should be equalized across protected subgroup, satisfying the **separability** criteria  $R \perp A|Y$  via the constraints:

$$\mathbb{P}\{R = 1 | Y = 1, A = a\} = \mathbb{P}\{R = 1 | Y = 1, A = b\} \quad (2)$$

$$\mathbb{P}\{R = 1 | Y = 0, A = a\} = \mathbb{P}\{R = 1 | Y = 0, A = b\} \quad (3)$$

In comparison to independence, separability states that algorithm scores should be conditionally independent of the protected attribute given the ground truth label. As a result, Equalized Odds considers that subgroups can have different distributions of  $P(Y)$  and is incentivized to reduce errors uniformly across all subgroups.

*c. Predictive Quality Parity.* Predictive Quality Parity asserts that the predictive positive and negative values should be equalized across subgroups, satisfying the **sufficiency** criteria  $Y \perp R|A$  via the constraint:

$$\mathbb{P}\{Y = 1 | R = r, A = a\} = \mathbb{P}\{Y = 1 | R = r, A = b\} \quad (4)$$

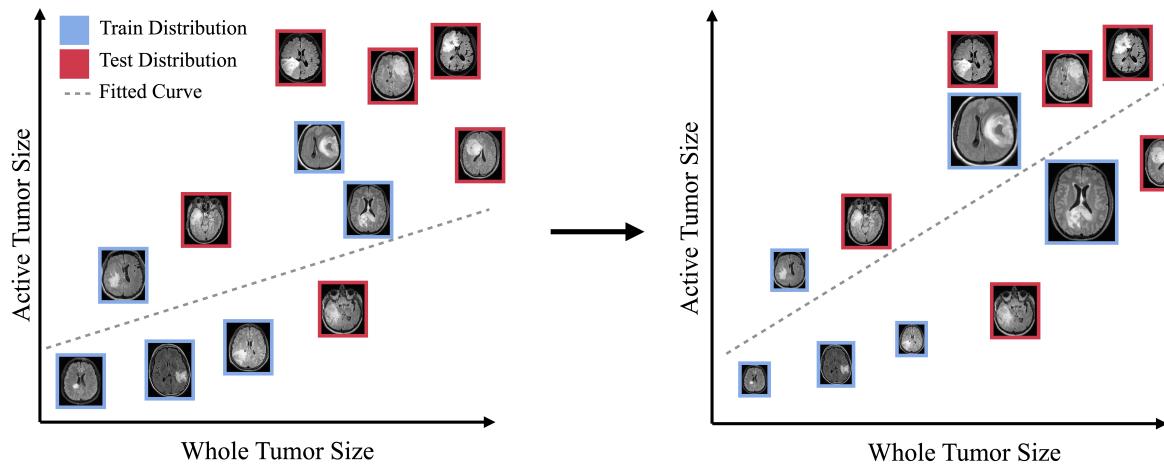
For unthresholded scores, Predictive Quality Parity can be viewed as a form of "calibration by group" in which for score  $r$  in the support of  $R$ , the following calibration constraint is satisfied for all subgroups in  $A$ :

$$\mathbb{P}\{Y = 1 | R = r, A = a\} = r, \quad \forall a \in A \quad (5)$$

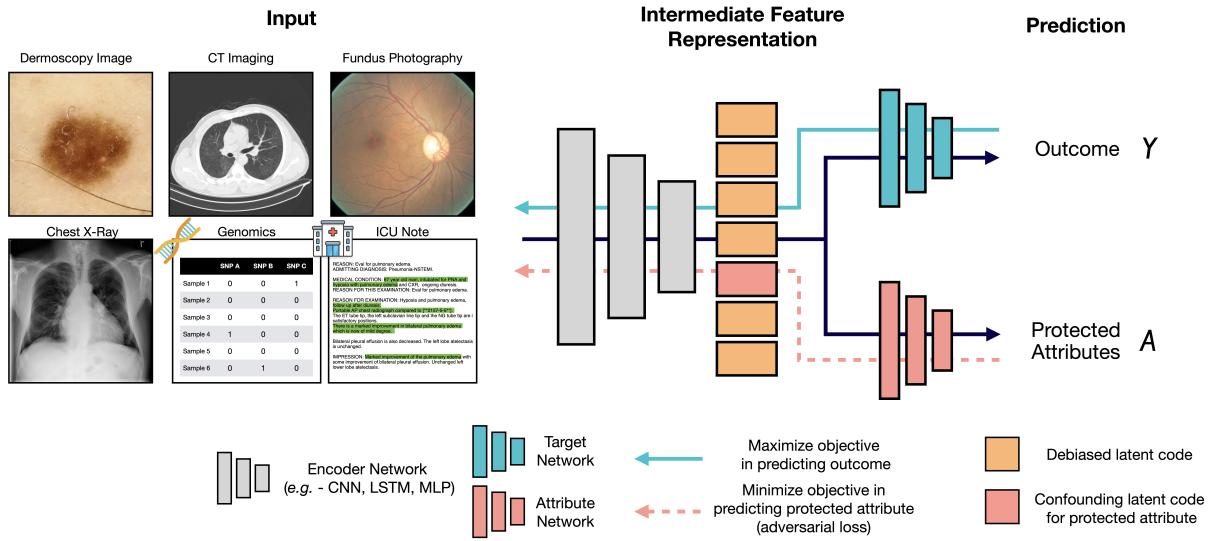
*Constraint Optimization.* As suggested, constraint optimization approaches typically include a non-discrimination term in the learning objective of models such as logistic regression classifiers and support vector machines to fulfill disparate impact and treatment mitigation<sup>45–47, 102, 103</sup>. In logistic regression models, loss terms can be created via computing the covariance of the protected attributes with the signed distance of the sample’s feature vectors  $X$  to the decision boundary, or modifying the decision boundary parameters to maximize fairness (minimizing disparate impact or mistreatment) subject to accuracy constraints<sup>46</sup>. Modifications to stochastic gradient descent have also been proposed to weigh fairness constraints in online learning as well<sup>104</sup>. A large limitation in constraint optimization approaches is that the learning objective is made non-convex in including additional non-discriminatory terms, which have been shown to reduce performance in comparison to simple reprocessing techniques such as resampling and importance weighting.

*Adversarial Fair Learning.* Adversarial fair learning focuses on learning an intermediate feature representation via deep learning that retains information from input space  $X$  without any features that correlates with  $A$ , as seen in **Figure 1**. Adversarial learning was first proposed in the minimax objective of Generative Adversarial Networks (GANs), in which a generator network learns to produce realistic image samples from an adversarial loss computed by a discriminator network<sup>105</sup>. In dataset shift, adversarial learning was also used as an adversarial domain adaptation approach, which aims to learn domain-invariant features of the train and test distribution, *e.g.* -  $P_{\text{train}}(Y|X) = P_{\text{test}}(Y|X)$ <sup>106</sup>. In fairness, such loss functions have been reused to learn race/ethnicity-invariant features via adversarial fairness, for removing disparate impact of deep learning models for a variety of tasks<sup>40, 107–114</sup>. As an unsupervised learning approach, LAFTR (Learned Adversarial Fair and Transferable Representations) was one of the first methods for fair dimensionality reduction, and demonstrated fair representations (debiased of  $A$ ) can be freely transferred to other domains without constraints on downstream classifiers as being fair<sup>115, 116</sup>. LAFTR proposed using adversarial regularization loss that augments the minimax GAN objective to make the latent feature representation invariant to protected class. Moreover, LAFTR also showed that such representations are transferrable, as examined the problem of Charlson Index prediction from insurance claims and physician records in the Heritage Health dataset, in which LAFTR able to transfer to other tasks without leaking sensitive attributes<sup>115, 116</sup>. Across other tasks in medicine, the novelty of LAFTR can be extended as a privacy-preserving machine learning approach that allows the transfer of useful intermediate features, which could advance multi-institutional collaboration in fine-tuning algorithms without leaking sensitive information. Similar to LAFTR are methods in unsupervised fair clustering, which further evaluates the fairness of debiased representations (via adversarial learning) in achieving attribute-invariant cluster assignments. However, a key limitation in many of these constraint optimization and adversarial fairness approaches is that it depends on having the protected class attribute at-hand in the train distribution, which

### a. Importance Weighting



### b. Fair Adversarial Learning



**Figure 1. Strategies for mitigating disparate impact.** **a.** For under-represented samples in the train and test distribution, importance weighting can be applied to reweight the infrequent samples to match the distributions. Mismatches in train and test distribution may occur in deploying an algorithm in a population with different demographics, disease prevalances, and sample selection biases that result in label prejudice. **b.** To remove protected attributes in the representation space of structured data modalities such as images and text data, deep learning algorithms can be additionally supervised with the protected attribute as a target label, in which the loss function for attribute prediction is maximized. Such strategies are additionally referred to as debiasing. In clinical machine learning tasks, modalities such as fundus photography images or chest X-ray images have been shown to include subtle biases that may leak protected attribute information such as age, gender, and self-reported race.

may not be possible in many practical situations in which protected class identity such as ethnicity is secured in many healthcare systems.

## Post-processing

Calibration is a post-processing technique used to satisfy sufficiency in fairness, and is applied to equalize the proportion of positive predictions to that of true positives in classification problems (Predictive Quality Parity). As demonstrated in **Box 1**, calibration is applied across all protected subgroups to ensure that probability estimates carry the same meaning across subgroups. As a risk tool, calibration theoretically allows risk estimates to have the same independent effectiveness regardless of group membership as seen in COMPAS. Despite this desirable role in risk assessment, calibration has been extensively studied and demonstrated to not always imply non-discrimination<sup>38</sup>. For instance, redlining in banking is an example of a calibrated algorithm that strategically misclassifies individuals with the intention of discrimination<sup>33</sup>. Calibration has also been shown to be incompatible with alternative definitions of fairness such as equalized odds and disparate impact outside of highly constrained cases<sup>49,50</sup>. To reconcile error parity and calibration, withholding predictive data for randomized inputs is often used as a post-processing step<sup>49,117</sup>. However, the exclusion of individual predictions and trade-off in model accuracy highly disfavor the use of this method in criminal justice and healthcare systems. Growing literature has begun exploring complementary concepts in fairness such as multi-calibration, an approach that focuses on identifiable subpopulations of individuals rather than large sets of protected groups. By using small samples of training data, multi-calibration situations where predictions at an individual level are considered the most fair<sup>118,119</sup>.

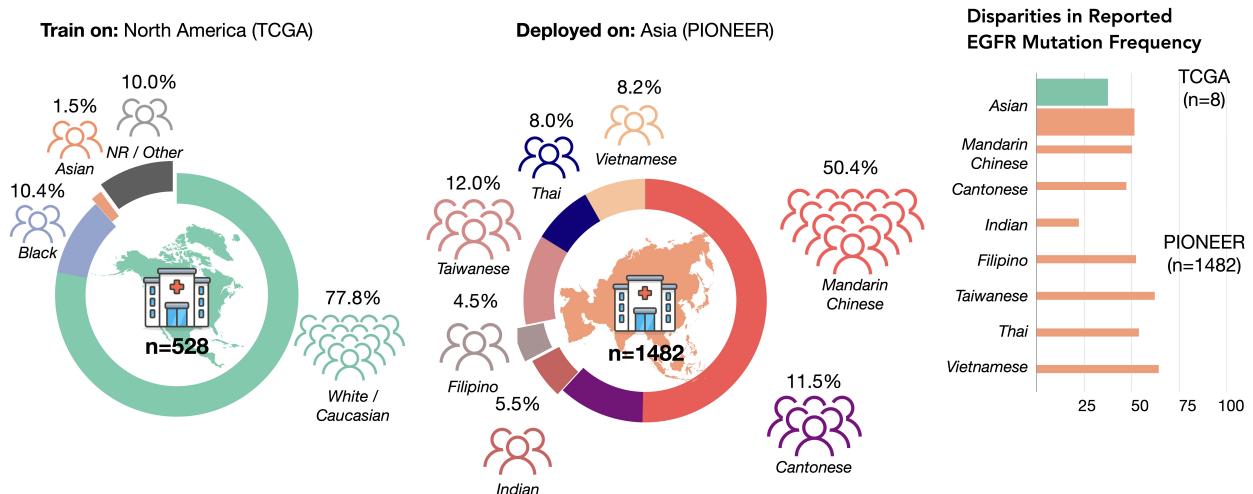
## Emerging Challenges in AI-SaMD Deployment

Current techniques for satisfying group fairness have largely revolved controlling for unwanted confounders that leak information about the protected subgroups, with strong assumptions placed that the training and testing dataset are independently and identically drawn (i.i.d.) from the same distribution. Though satisfying notions of fairness on the training dataset, algorithms that forget to consider dataset shift at deployment time may still have disparate performance on the test dataset. Dataset shift occurs when there is a mismatch between the training and testing distribution during algorithm development, and is a re-occurring phenomena in medical AI as a result of differences such as population demographics and genetics, image acquisition techniques, disease prevalence, and social determinants of health<sup>10,123–125</sup>. For instance, in developing an AI algorithm trained on cancer pathology data from the United States and deployed on data from Turkey, domain

Data	Machine Learning Task	Issue in Fairness	Dataset Shift	Mitigation Strategy
Clinical Lab Measurements	Predicting Kidney Failure using eGFR equation  Checking for uterine track infection  Predicting Osteoporosis using a bone fracture risk calculator  Estimating lung function via forceful exhalation of a spirometer (VBAC calculator)  Opiod Early Warning System.	Race-specific covariate bias kidney function appear better in Black patients, which could delay medication and referrals for precluding kidney failures <sup>17</sup> .  Race-specific covariate bias assigns lower odds of checking checked for UTI in black patients, reduces likelihood of scheduling follow-up and referrals <sup>120</sup> .  Race-specific covariate place black women at lower risk of osteoporosis, while high-risk patients receive preventative drugs to minimize fractures <sup>121</sup> .  Race-specific covariate delay diagnosis of lung disease in black patients <sup>120</sup> .  Changing from ICD-9 to ICD-10 resulted in a large wave of false negatives and a much higher prevalence of opioid-related codes <sup>122</sup> .	Population Shift  Label / Annotation Shift	Race Exclusion, Constraint Optimization, Model Calibration  Model Calibration
Pathology	Cancer Diagnosis, Cancer Prognosis, Organ Rejection Prediction	Lack of race/ethnicity-stratified evaluation of AI-SaMDs due to poor data interoperability, which results in poor algorithm fairness evaluation.  Underserved patients with poor access to health care may developed more poorly-differentiated and invasive grade tumors due to delayed biopsies, leading to unconscious algorithm biases.  Model Leakage of self-reported ethnicity information due to site-specific staining techniques, leaking to poor generalization to external cohorts <sup>29</sup> .  Only patients developing symptoms will be biopsied, which produces disparities in patients who will get pathology services due to access to care, leading to dataset imbalance.	Population Shift  Domain / Acquisition Shift  Sample Selection Bias	Federated Learning  Federated Learning, Importance Weighting  Adversarial Regularization  Federated Learning, Importance Weighting

Genomics	Mutation Prediction	Genetic variation amongst patients of different ancestry and ethnicity, located in different geographical locations with additional local environmental factors, results in different phenotypes, leading to classification disparities in inferred mutation prediction <sup>55</sup> .	Population Shift	Race Inclusion
	Polygenic Risk Scores	Variations in linkage disequilibrium structures and minor allele frequencies across ancestral populations contributes to worse performance of genetic polygenic risk models in Black populations <sup>58</sup> .	Population Shift	Federated Learning
Radiology	Disease Segmentation and Detection in MRI / CT / Chest X-Ray / Mammography Scans	AI algorithms trained on publicly-available radiology images misdiagnose under-served patients at a disproportionate rate compared to the baseline population <sup>30</sup> .	Population Shift	Federated Learning, Importance weighting
		Model leakage of self-reported ethnicity information after controlling for site-specific technical artifacts and potential anatomic differences <sup>101</sup> .	Unknown	Disentanglement of Causal Factors *
		Under-served patients with poor access to health care may developed more poorly-differentiated and invasive grade tumors due to delayed biopsies, leading to unconscious algorithm biases.	Population Shift	Federated Learning, Importance weighting
Dermatology	Skin Lesion Segmentation and Detection	Google dermatology app originally had no dark brown/black skin types in dataset, which may over- or under-diagnosis non-White patients with under-represented Fitzpatrick skin types.	Population Shift / Sample Selection Bias	Federated Learning, Importance Weighting
Ophthalmology	Retinopathy Grading, Risk Assessment, and Vessel Segmentation	Fundus photography images have recently been shown to predicting risk factors such as age and gender, which may contribute towards disparate treatment in cardiovascular risk assessment.	Unknown	Importance Weighting
		Differing clinical education in training ophthalmologists, as well as inherent intraobserver variability, results in different segmentation results of pathological features such as soft and hard exudates.	Label / Annotation Shift	Federated Learning, Model Calibration
Rheumatology	Predicting Pain and Surgery Eligibility	Disparities in how self-reported race and ethnic population respond to pain, may bias algorithms trained on reported pain score <sup>23</sup> .	Label / Annotation Shift	Importance Weighting, Model Calibration

**Table 2. Examples of algorithm unfairness, their associated dataset shift, and mitigation strategies.**



**Figure 2. Genetic drift as population shift.** Demography characteristics and gene mutation frequencies for EGFR of lung adenocarcinoma patients in the TCGA (green) and PIONEER (orange) cohort. Of the 528 lung adenocarcinoma patients in the TCGA, only 1.5% ( $n = 8$ ) self-report as "Asian", versus the 1482 Asian patients enrolled in PIONEER, which includes a more fine-grained self-reported ethnicity / nationality categorization of: Mandarin Chinese, Cantonese, Taiwanese, Vietnamese, Thai, Filipino and Indian. As a result of under-representation of Asian patients in the TCGA, the mutation frequency for genes such as EGFR, which is commonly used in guiding the use of TKIs as treatment, is only 37.5% ( $n = 3$ ). In PIONEER, overall EGFR mutation frequency for all Asian patients was found to be 51.4% ( $n = 653$ ), with differing mutation frequencies found across different ethnic subpopulations.

shifts as a result of H&E staining protocols, as well as population shifts due to imbalanced ethnic minority representation, may cause the model to severely misdiagnose Turkish cancer patients. In other cases, hospitals may operate with different ICD systems, which results in label shifts in how algorithms are evaluated<sup>122, 126</sup>. Overall, algorithms that would be sensitive to dataset shift during deployment, may also be prone to exacerbating healthcare disparities and under-perform on fairness metrics. With access to ground truth labels normally unavailable at test time, their are also limitations in how AI models can be fairly evaluated at all in real-world clinical settings. In this section, we examine several domain-specific challenges in current AI deployment in healthcare from the perspective of group fairness and dataset shift, illustrated for the case of pathology in **Figure 2** and **Figure 3**. A high-level overview of dataset shift with examples in medicine can be found in **Table 2**, with a formal introduction referred to other literature<sup>123, 127</sup>.

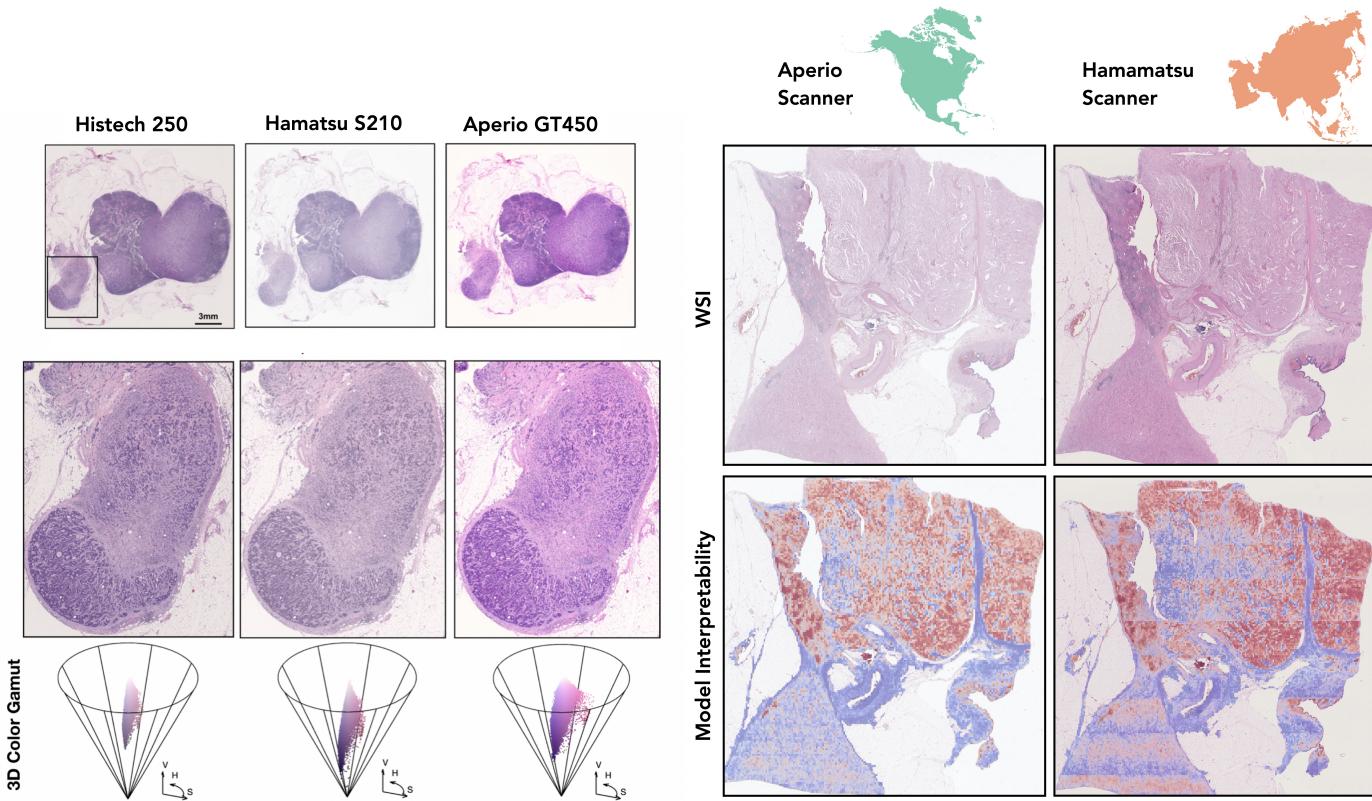
### Missing Ethnic and Ancestral Diversity in Biomedical Datasets

In the current development and integration of AI-based computer-aided diagnosis (CAD) systems in healthcare, the vast majority of models are trained on race-skewed datasets that over-represent individuals of European ancestry, with race-stratified evaluation largely ignored in reporting precision and recall. Moreover, much of our

understanding of many diseases has been developed using biobank repositories that predominantly represent individuals with European ancestry<sup>53, 128, 129</sup>. Ethnicity, along with other demographic data, is a crucial determination of the mutational landscape and the pathogenesis of cancer, with the prevalence of certain mutations only detectable in high-throughput sequencing of large and representative cohorts<sup>130</sup>. For instance, individuals with Asian ancestry are known to have a high prevalence of EGFR mutations as detected in the PIONEER cohort that enrolled 1482 Asian patients (**Figure 2**)<sup>55</sup>. However, in the The Cancer Genome Atlas (TCGA), across 8,594 tumor samples from 33 cancer types, 82.0% of all cases were from Whites, 10.1% were from Blacks or African Americans, 7.5% were from Asians, and 0.4% from extremely under-reported minorities such as Hispanics, Native Americans, Native Hawaiians and other Pacific Islanders (denoted as "Other" in the TCGA) (**Figure 2**)<sup>131</sup>. As a result of population shift, many common genomic alterations such as EGFR (discovered by other high-sequencing efforts) are undetectable in the TCGA, which has been extensively used to discover molecular subtypes and redefine World Health Organization (WHO) taxonomies for cancer classification<sup>132, 133</sup>. In other areas of precision medicine research, variations in linkage disequilibrium structures and minor allele frequencies across ancestral populations contributes to worse performance of genetic polygenic risk models in Black populations<sup>56, 57, 134–137</sup>.

Despite these disparities in representation, many AI algorithms undergoing "clinical-grade" validation are trained and evaluated on race-skewed, public biobank datasets without considering their disparate impact on minority subpopulations due to population shift. For instance, the first AI models to surpass clinical-grade performance on predicting lymph node metastases were trained and evaluated on the CAMELYON16/17 datasets sourced entirely from the Netherlands<sup>138, 139</sup>. However, such algorithms have yet evaluated race-stratified performance due to a lack of large and ethnic-diverse external cohorts. For cancer types such breast cancer in which there is known genetic diversity in hormone receptor status amongst ethnic subpopulations, phenotypic manifestations of genetic diversity may leak ethnicity subgroup information in diagnostic algorithms<sup>140–144</sup>. In this example, ancestry and genetic variation are latent variables that may manifest in the tissue microenvironment, which poses a challenge in the representation space and would thus entail debiasing strategies such as adversarial learning or regularization. Many attempts in establishing histology-genomic correspondences have also been only accomplished using the TCGA and other European biobanks, which makes computational pathology and genomics a challenging domain in dataset shift and model calibration<sup>145–147</sup>.

In some applications, it may also be beneficial to include protected attributes such as ethnicity into algorithms, especially when the target label is inferring genetic variation which is correlated with ancestry. One of the most promising deep learning applications in pathology and genomics integration is mutation predic-



**Figure 3. Dataset shift in AI-SaMD deployment for a clinical-grade pathology AI algorithm.** Examples of site-specific H&E stain variability under different whole slide scanners, and their downstream affect on attention-based heatmaps of weakly-supervised AI algorithms in model audit.

tion from Whole Slide Images (WSIs), which if successful can be adopted as a low-cost, screening approach for inferring genetic aberrations without high-throughput sequencing<sup>148</sup>. A direct clinical application of deep learning-based mutation prediction is to predict biomarkers such as microsatellite instability (MSI), an FDA-approved biomarker for guiding the use immune-checkpoint inhibition therapy, or EGFR in guiding treatment of multiple tyrosine kinase inhibitors (TKI) in lung cancer<sup>145</sup>. However, such an approach trained on TCGA and evaluated on the PIONEER cohort may predict low EGFR mutation frequency and misguide Asian patients with incorrect cancer treatment strategies, even with strategies such as importance weighting as the demography size for protected subgroups may be too minuscule. In this particular instance, using protected class information such as ancestry as a conditional label may improve performance on mutation prediction tasks. At the moment, there is no current work on disentangling genetic variation and measuring the contribution of ancestry towards phenotypic variation in the tissue microenvironment, which is precluded by a lack of large, publicly-available, and also multimodal biobank data.

## Image Acquisition and Measurement Variation

In addition genetic drift in the population, variations in image acquisition and biological measurement techniques can also be confounders that leak protected class information. This type of covariate shift is known as domain (or acquisition) shift, in which patients with the same underlying phenotype and annotation may still vary due to institution-specific protocols and other non-biological factors that affect data acquisition<sup>127</sup>. For example, in radiology, collected X-Ray, mammography, or CT imaging data may vary due to radiation dosage which affects the signal-to-noise ratio in producing the image. In pathology, there is also enormous heterogeneity in tissue preparation and staining protocols, as well as scanner-specific camera parameters for slide digitization, which has been shown to affect model performance in slide-level cancer diagnostic tasks (**Figure 3**).

Though medical domain shift is a well-recognized problem, domain shift as a result of site/region-specific factors that correlate with demographic characteristics may also introduce spurious associations with ethnicity. For example, a recent audit study assessing site-specific stain variability of pathology slides in the TCGA found shifts in stain intensity in University of Chicago, which notably was the only site with a greater prevalence of patients with African ancestry<sup>29</sup>. As a result, many of the aforementioned clinical-grade AI algorithms in pathology may be learning inadvertent cues for ethnicity via institution-specific staining patterns. In this instance of domain shift, variable staining intensity can be corrected using domain adaptation and optimal transport techniques that adapt the test distribution to the training dataset, which can be performed on either the input or representation space. For instance, recent deep learning techniques using generative adversarial networks have been able to learn stain features as a form of style transfer, in which a GAN can be used to preprocess data at deployment time to match the training distribution<sup>106,149</sup>. Other in-processing techniques such as adversarial regularization can be leveraged to learn domain-invariant features using semi-supervised learning using samples from both the training and test distributions. However, a practical limitation in both mitigation strategies is that the respective style-transfer or gradient-reversal layers would need to be finetuned with data from the test distribution for each deployment site, which can be challenging due to stagnant data interoperability between institutions as well as regulations for refining AI-SaMDs<sup>31</sup>. In some applications, disentangling sources of shift presents a challenge in developing bias mitigation strategies that would remove confounding non-biological factors. For instance, despite no known anatomic and phenotype population features in radiology, recent work has found that CNNs can reliably predict race in chest X-ray and radiology images despite controlling for image acquisition factors, removing bone density information and severe degradation of image quality using low- and high-pass filtering<sup>101</sup>.

## Evolving Dataset Shifts Over Time

In medicine, dataset shift can occur also as a result from changes in technology, population and environment, and human behavior over time<sup>150</sup>. Canonical examples include the migration from ICD-8 to ICD-9 with reclassified the refactored the coding for "surgical" procedure, or the migration from ICD-9 to ICD-10 which created a large spike in opioid-related inpatient stays<sup>122, 126</sup>. A more recent example of label shift is seen with the Epic Sepsis Model (ESM), a sepsis prediction model that was deactivated in April 2020 due to the changes in patient demographic characteristics confounded by the onset of COVID-19. To mitigate dataset shifts, proposed guidelines have emphasized the importance of guaranteeing model stability to how the data were generated<sup>125</sup>, with reactive and proactive approaches for intervening on temporal dataset shift in active, early-warning systems such as sepsis prediction<sup>124, 151</sup>.

In the context of fairness, such shifts are difficult to avoid as available data may have been generated through an inherently discriminatory process. Moreover, evaluation of fairness metrics may be difficult at deployment time without access to the test labels, which may further be exacerbated with annotation shift in: 1) intra-observer variability amongst clinicians and 2) evolving clinical knowledge. To date, most work has focused on fine-tuning static pre-trained fair classifiers using few-shot learning, or developing new fairness measures that address short- and long-term decision-making with multi-task objectives<sup>152–154, 154, 155, 155</sup>. At the moment, however, analyses of fairness metrics under temporal dataset shift has not yet been examined in current AI-SaMDs.

## Fragility of Race

Similar to the problem of label shift across train and test distributions, different geographic regions and countries may collect protected attribute data with varying levels of stringency and granularity. One issue that complicates the incorporation of race as a covariate in evaluations of fairness of medical AI models is the active evolution of the medical community's understanding of race itself<sup>156</sup>. As discussions regarding race and ethnicity have moved more into the mainstream, the medical community has begun to realize that the racist taxonomies of the past do not adequately represent the groups of people that they purport to. Indeed, it is now accepted that race is a social construct and that there is greater genetic variability within a particular race than there is between races<sup>157–159</sup>. As such, categorization of patients by race can obscure a host of potential confounders to fairness analyses including culture, history, and socioeconomic status that all may separately and synergistically influence a particular patient's health<sup>160, 161</sup>. These manifold factors can also vary by location

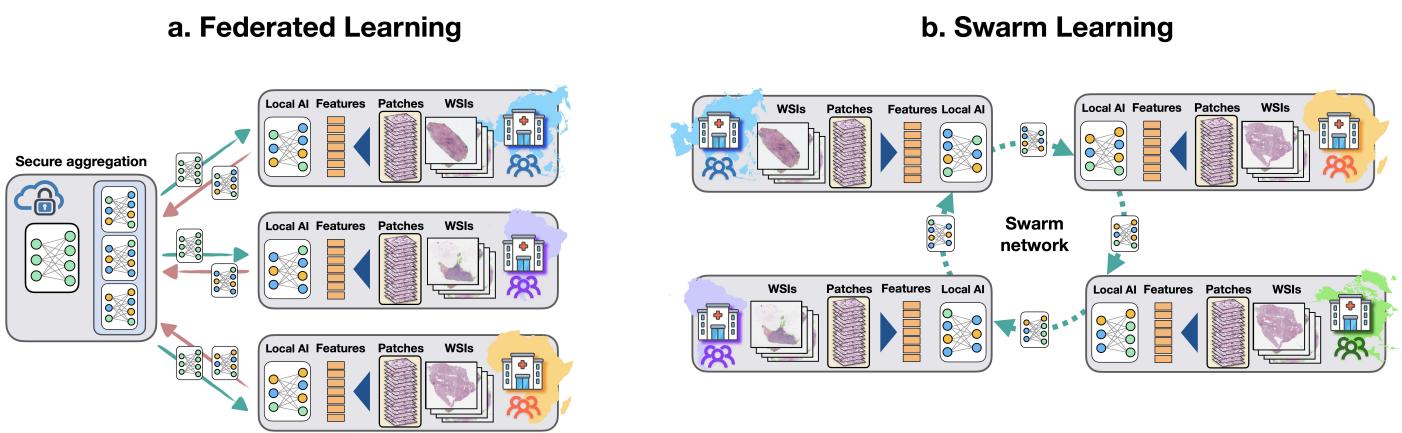
so that the same person may be considered of different races in different geographic locations, as seen in the example of self-reported Asian ethnicity in the TCGA versus Pioneer and self-reported race in COMPAS<sup>55, 161</sup>.

Ideally, discussions should center explicitly around each component of race and include ancestry, a concept with a clear definition (the geographic origins of one's ancestors) and one more directly connected to the patient's underlying genetics. Unfortunately, introducing this granularity to fairness evaluations has clear drawbacks in terms of the power of subgroup analyses and this data is not routinely gathered on patients at most institutions which often fall back on the traditional dropdown menu that allows one to select only a single race and/or ethnicity. Performing fairness evaluations without explicitly considering these potential confounders of race may mean that the AI system under study is sensitive to some unaccounted-for factor hidden from the analysis<sup>160</sup>.

## Paths Forward

### Distributed Learning to Overcome Unfair Dataset Shift

Unlike machine learning performed over a centralized pool of training data, federated learning is a distributed learning paradigm in which, loosely speaking, a network of participating users utilize their own compute resources and local data to collectively train a global model stored on a server<sup>162–165</sup>. This way, users in principle retain oversight of their own data and instead only have to share the update of weight parameters or gradient signals from their locally trained model with a central server. As a result of privacy-preserving guarantees in training machine learning algorithms without centralized data, federated learning paradigms have been applied to a wide variety of tasks in medicine in: 1) overcoming data interoperability standards that would usually prohibit sensitive health data from being shared; 2) eliminating low data regimes of clinical machine learning tasks that predicting rare diseases (**Figure 4a**)<sup>85, 166–180</sup>. For example, in EMR data, federated learning has been previously demonstrated in satisfying privacy-preserving guarantees for transferring sensitive health data, as well as developing early warning systems for hospitalization, sepsis, and other preventive tasks<sup>175, 181</sup>. In radiology, federated learning has been recently used for multi-institutional collaboration and validation of AI algorithms for prostate segmentation, brain cancer detection, and monitoring Alzheimer's disease progression from MRI scans, as well as classification of paediatric chest X-ray classification under various network architectures, privacy-preserving protocols, and ablation studies to adversarial attacks<sup>171, 174, 182–184</sup>. In pathology, model audit studies have assessed the robust performance of weakly-supervised algorithms for WSIs under various



**Figure 4. Enabling multi-institutional collaboration via decentralized learning.** **a.** A proposed federated learning framework in training with multi-institutional cohorts from various countries, each distributed client shown as a country with weigh updates made to a central server. **b.** A proposed swarm learning framework in which weigh updates are made over edge layers using blocktrain contracts, which precludes communication with a central server.

privacy-preserving noise levels in diagnostic and prognostic tasks<sup>185</sup>. As a result of the SARS-CoV-2 pandemic in 2019, federated learning has been employed overcoming low sample sizes of COVID-19 pathology in AI model development, as well as independent test cohort evaluation<sup>186–188</sup>.

With respect to fairness, federated learning paradigms for decentralized AI-SaMD development has been demonstrated to have a directly mitigate disparate impact via model development on larger and more diverse patient populations<sup>58</sup>. For instance, In the case of population shift as a result of genetic variation, decentralized information infrastructure have been previously proposed to harmonize biobank protocols and developed tangible material transfer agreements amongst three hospitals, which demonstrates the potential applicability of federated learning paradigms in developing large and diverse biobank data for diverse populations<sup>189</sup>. In developing polygenic risk scores, federated learning has been used as an integration strategy in merging heterogeneous population data from multiple healthcare institutions, with subsequent validation of federated models on underrepresented populations<sup>58,190</sup>. In the previous examples of site-specific staining variability across different hospital sites, federated learning can be used to train decentralized models that are invariant to stain via domain generalization, as well as domain adaptation in refining AI-SaMDs locally to the test data distribution with minimal updates<sup>29</sup>. Many of the current research directions in federated learning point towards multi-site domain adaptation across distributed clients<sup>191–195</sup>. For instance, Federated Multi-Target Domain Adaptation (FMTDA) is a task that addresses domain gaps between unlabeled, distributed client data and labeled, centralized data over the server, as well as degraded performances of federated domain adaptation methods<sup>196</sup>.

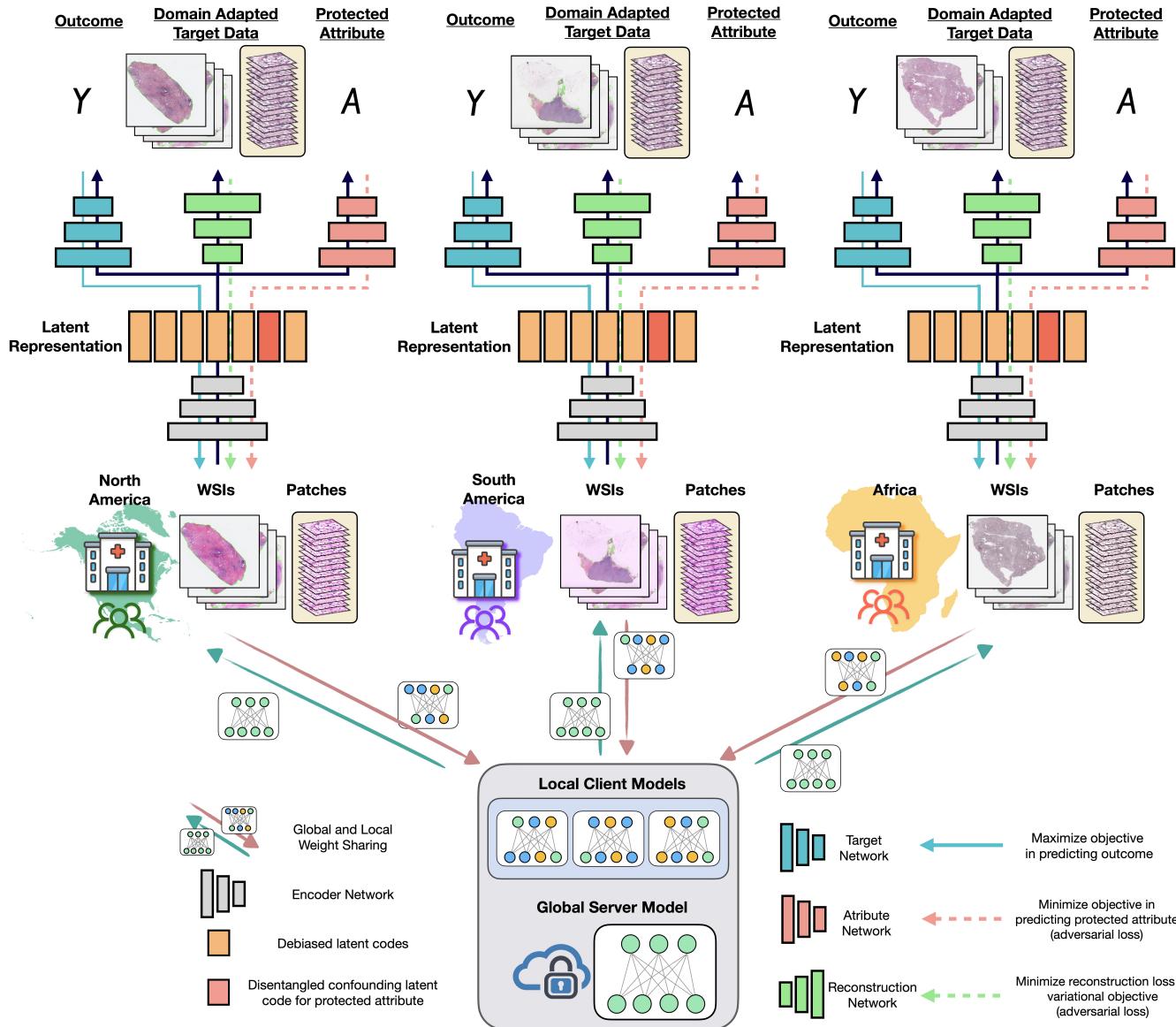
Though federated learning may overcome data interoperability standards and enable training AI-SAMDs

with diverse cohorts, the evaluation of AI biases in federated learning settings is yet to be extensively studied. Despite numerous technical advances made in improving communication efficiency, robustness and security of parameter updates, one of the key statistical challenges is learning from non-i.i.d data, which arises due to the sometimes vast differences in local data distribution at contributing sites, which can lead to the divergence of local model weights during training following a synchronized initiation of model weights<sup>164, 197–199</sup>. Accordingly, the performance of FL algorithms, including the well-known FedAvg algorithm<sup>200, 201</sup> that uses averaging to aggregate local model parameter updates has been shown to deteriorate substantially when applied to non-i.i.d. data<sup>202</sup>. Such statistical challenges may produce further disparate impact depending on heterogeneity of data distributions across clients. For instance, in using multi-site data in the TCGA as individual clients for federated learning, for the TCGA Invasive Breast Carcinoma (BRCA) cohort, a majority of parameter updates would come from clients that over-represent individuals with European ancestry, with only one parameter update coming from a single client that has majority representation for African ancestry. For decentralized training with diverse biomedical datasets, an important consideration is thus the added complexity in disentangling the impact of site-specific dataset shift from non-i.i.d. data on algorithm fairness, which will not only be problem-specific but also highly-variable from the collaboration structure of participating institutions from differing geographic locations. Moreover, federated learning models can still be affected by biases in the local dataset of each participating client or institution, as well as other variables such as the weighted contribution of each site in updating the global model and the varying frequencies at which different sites participate in training<sup>203</sup>. In the previous example of multi-site data from the TCGA-BRCA cohort, federated models would be subject to site-specific biases such as H&E stain intensity, intra-observer variability, ethnic minority under-representation found in centralized models<sup>29</sup>. Though federated learning would enable the application of finetuning AI-SaMDs per deployment site, race/ethnicity-evaluation of federated models has yet to be benchmarked. Lastly, access to protected attribute data in each site may still pose an issue in fairness evaluation, as sensitive information such as race and ethnicity are typically isolated in separate databases and may produce additional logistic barriers despite interoperability.

A final but important consideration in the practical adoption of fair and federated learning paradigms is the current difficulty for practitioners in operationalizing fairness principles for much simpler AI development and deployment life-cycles of centralized models. In current organizational structures, the roles and responsibilities created for implementing fairness principles are typically isolated into: 1) practitioner / "data regulator" roles, which design AI fairness checklists for guiding the ethical development of algorithms in the organization, and 2) engineer / data user roles, which follow the checklist during algorithm implementation<sup>204</sup>. Though intuitive, such binary roles may have poor efficacy in practice, as fairness checklists are often too

broad, abstractive, and not co-designed with engineers in addressing problem-specific, technical challenges for achieving fairness<sup>205</sup>. In the consideration of federated learning paradigms for AI-SaMD development and deployment, the design of fairness checklists would require not only interdisciplinary collaboration from all healthcare-related roles (*e.g.* clinicians, ethics practitioners, engineers, researchers), but also further involvement from stakeholders at participating institutions in identifying potential site-specific biases that may be propagated during parameter sharing. Similar to the problem of label / annotation shift that may occur at various sites, the design of a global fairness checklist has additional complexity in considering culture-specific factors within each geographic region that would affect access to protected information, as well as definitions and criteria for fairness from differing moral and ethical philosophies<sup>206</sup>.

Though access to protected attributes may pose an issue in model evaluation at local sites, a potential advantage that may benefit the design of fair and federated models is that the geography of the client identities may be used as proxy variables for subgroup identity, which may inform the development of novel fairness techniques without access to sensitive information. Recent decentralized frameworks have demonstrated that federated learning, in combination with GAN-based fair representation learning methods such as LAFTR, can be used to learn federated, adversarial, debiasing (FADE) representations with similar privacy-preserving and transferable properties as LAFTR, and was benchmarked on mild cognitive impairment detection from sensor data<sup>207</sup>. In comparison to other paradigms, FADE has a unique property in that protected attributes are not needed to learn invariant representations, in that the client identities are instead used during adversarial regularization. In application to other areas of fairness, data preprocessing strategies such as importance weighting can potentially be developed to reweight not only infrequent samples, but also model updates from clients containing only under-represented minority subpopulations. In addition, fairness evaluation criteria can potentially be evaluated at the client-level, which may contribute towards developing novel in-processing and post-processing techniques without knowledge of protected attributes. In instances such as multi-site TCGA data which leak ethnicity subgroup membership largely due to the correlation of sample selection bias and H&E stain variability, many fairness evaluation criteria and post-processing techniques can potentially be performed at the client-level without detailed knowledge of patient demography. In training with heterogeneous data sources, such an assumption may hold for many clinical tasks as geography has been shown to be a closer link to genetic diversity than ethnicity<sup>208</sup>.



**Figure 5. A decentralized framework that integrates federated learning with adversarial learning and disentanglement.** In addition to developing algorithms on larger and more diverse patient populations, federated learning can also be integrated with many current techniques in representation learning and unsupervised domain adaptation that can additionally learn with unobserved protected attributes. In FADE, the client IDs are used as protected attribute, with adversarial learning used to debias the representation to be invariant to geographic region (attribute network branch, colored red)<sup>207</sup>. In FedDis, disentanglement was used to disentangle shape and appearance features in brain MRI scans, with only the shape parameter shared between clients (disentangled representation, colored orange)<sup>209</sup>. In FADA, disentanglement and adversarial learning can be used to further mitigate domain shift across clients (both attribute network branch and disentangled representation, colored red and orange)<sup>210</sup>. Federated learning can also be used in combination with style transfer, synthetic data generation, and image normalization in which domain adapted target data would need to be shared (reconstruction network branch, colored green)<sup>210–213</sup>.

## Fair Representation Learning via Disentanglement

Tangential to the work of unsupervised fair representation learning in LAFTR and FADE is disentanglement in generative models, which can also be used to further promote fairness in learned representations without access to protected attributes. Disentanglement is a growing research subfield within representation learning which aims as disentangling independent and easy-to-interpret factors of data in the latent space, and has demonstrated success in isolating sources of variation of objects such as color, pose, position, and shape<sup>214–218</sup>. The first method to demonstrate and quantify disentanglement in deep generative model was BetaVAE, which uses a variational autoencoder (VAE) bottleneck for unsupervised learning, followed by proposing a disentanglement score via training a linear classifier to predict the fixed factor of variation from the representation<sup>218</sup>. Entropy-based metrics such as Mutual Information Gap (MIG), Modularity, Separated Attribute Predictability (SAP), and the Disentanglement-Completeness-Informativeness (DCI) framework have similar been proposed for quantifying pairwise mutual information of all possible individual latent codes in the representation<sup>216,219–222</sup>. In application to medicine, disentangled VAEs with adversarial loss components have been used in disentangling size, skin color, and eccentricity in dermoscopy images, with subsequent improvement found in clustering and skin lesion classification<sup>223</sup>. In longitudinal time-series data, VAEs with Guassian Priors have been used in disentangling physiological waveforms from causal health conditions and other anatomic factors<sup>224,225</sup>. Outside of VAEs, other unsupervised learning techniques such as GANs (*e.g.* - InfoGAN, BigBIGAN, StyleGAN) have achieved similar disentanglement-like properties while also demonstrating strong performance on downstream tasks<sup>226–228</sup>. In synthetic image generation for natural images, approaches such as StyleGAN are able to not only separate style from content in an image, but also achieve unsupervised separation of local- to high-level attributes (*e.g.* - stochastic variation of hair split ends to hair color) in performing fine-grained image editing. On brain MRI scans, approaches similar to StyleGAN have been used in performing feature disentanglement of 19/20 chromosomal gain<sup>229</sup>. In cardiac MRI and CT imaging, disentanglement has also been used in factorizing images into spatial anatomical factors and non-spatial modality factors with improvement found in multi-task segmentation, regression, and image-to-image synthesis tasks<sup>230</sup>.

In relation to fairness, disentanglement can be viewed as a form of data preprocessing that can de-bias datasets before model development. Similar to separating content and style in natural images, disentanglement can potentially be used as an unsupervised approach for isolating protected attribution information such as ethnicity, which can be subsequently truncated from the latent code for downstream fairness tasks<sup>?,231</sup>. Recent exhaustive studies on the evaluation of unsupervised VAE-based disentangled models have demonstrated

that disentanglement scores correlate with fairness metrics, benchmarked on numerous fair classification tasks without protected attribute information<sup>232</sup>. In application to face identification, disentanglement-like methods have been proposed in clustering human faces without latent code information that contain dominant features such as skin and hair color<sup>233</sup>. Though applicable in settings with unobserved protected attributes, disentanglement can also be used in conjunction with adversarial learning to enforce orthogonality constraints to force independence of protected and non-protected latent codes, similarly applied to faces<sup>234</sup>. In combination with federated learning, frameworks such as FedDis has been demonstrated to isolate sensitive attributes in non-i.i.d. MRI lesion data, in which images are disentangled into shape and appearance features with only the shape parameter shared between clients (**Figure 5**)<sup>209</sup>.

Within current development and deployment lifecycles for AI-SaMDs and other AI algorithms, the adaptability of unsupervised disentanglement methods can potentially be used in refining the distribution of responsibilities in organizational structures in also including the role of "data producers", who produce "cleaned" versions of the input that are still informative in downstream tasks and can further quantify fairness-accuracy trade-offs in using disentangled representations<sup>204</sup>. In this setting, the role of "data users" would be separated from that of "data regulators", which may allow conventional model development pipelines without considering additional fairness constraints. Such an approach may pave a path forwards for a novel three-party governance model that simplifies communication overhead in discussing concerns of accuracy-fairness trade-offs, and may adapt to test populations without the complexities introduced by federated learning which also needs access to protected attributes. However, a limitation for current application is that though current state-of-the-art methods perform well on disentanglement scores, methods using disentanglement have not bee demonstrated in reach competitive performance with other unsupervised learning techniques such as contrastive learning and student-teacher knowledge distillation methods<sup>235,236</sup>. Moreover, a large body of disentanglement approaches are only bench-marked on synthetic or semi-synthetic data that are generated in controlled settings. As an ongoing and promising research direction, future work into understanding disentanglement and adapting it robust self-supervised learning paradigms would contribute to improving fairness in transfer learning tasks, as well as also serving as a privacy-preserving measure that would be useful in clinical machine learning tasks.

## Model Auditing using Interpretability

In addition to measuring disparate impact, algorithm interpretability is an important goal in the fair, accountable and transparent machine learning (FATML) research community as it can be used as a tool for model auditing and mitigating sources of bias in dataset collection. Interpretability in deep learning algorithms has emerged as its own technical subfield in order to derive explanations from "black-box" algorithms, especially in learning applications that operate on structured data modalities such as images and text. In this subsection, we briefly review interpretability methods, and their role in fairness and medicine.

*Saliency Maps and Perturbations.* Saliency mapping is a class of methods that aims to find sensitive input features that would explain the decision made by a network. For images, the partial derivatives of the predictions with respect to pixel intensities computed during back-propagation of the network, which then produce a fine-grained visualization of informative image regions. Saliency maps were first proposed in visualizing image classification models, and have since inspired a wide class of methods such as Class Activation Maps (CAM)<sup>237</sup>. CAM methods such as Grad-CAM are layer attribution techniques that attributes how a neuron of an intermediate feature layer of a CNN would affect the output. The attributions for the targeted layer are then upsampled to the original image size and viewed as a mask to identify discriminative image regions<sup>238</sup>. Guided Grad-CAM overcomes the issue with non-negative gradients in standard back-propagation and Grad-CAM, where ReLU activations are overridden such that only non-negative gradients are back-propagated. Within the medical imaging community, CAM-based methods have gained widespread adoption in the interpretation of CNNs for clinical interpretability, as salient regions refer to high-level image features rather than low-level pixel intensities. Because these techniques can be applied without modifying the networks, existing and/or deployed models can be readily adapted to understand network predictions, and have since been used to audit models in various AI-based medicine applications such as skin lesion detection, chest x-ray disease localization, and CT organ segmentation<sup>23, 73, 100, 239–245</sup>. In tabular-structured clinical data such as genomic and transcriptomic features, similar gradient-based techniques such as Integrated Gradients have been developed for quantifying local- and global-level feature importances in corroborating the role of cancer-driving genes in cancer prognostication and single nucleotide polymorphisms (SNPs) in genome-wide association studies (GWAS)<sup>246–248</sup>. Tangent gradient-based methods are also perturbative-based techniques such as (*e.g.* - Occlusion, ArchDetect, Shapley Sampling), in which individual features are permuted to assess counterfactual feature importance<sup>249–254</sup>. To assess the quality of interpretability or retrieved feature importance results, frameworks such as Remove and Retrain (ROAR) propose masking different thresholds of important

features followed by retraining and model evaluation, in which masked importance features should degrade performance<sup>255,256</sup>.

*Attention-based interpretability.* In comparison to gradient-based methods, attention-based methods require direct modifications to the neural network to implement a Softmax activation function that computes a probability weight distribution over the inputs, which are used as feature importance and subsequent interpretability<sup>257,258</sup>. Attention-based interpretability is typically designed for network architectures that operate over set-based data structures (*e.g.* - bags of word embeddings, single cell features, image patch embeddings), in which for a bag of feature embeddings  $\mathbf{x} = \{x_1, \dots, x_n\}$ , the network computes a normalized score  $\mathbf{w}$  such that  $\sum_i^N w_i = 1$  using Softmax activation<sup>257</sup>. During training and evaluation, these scores are used as weights in permutation-invariant set aggregation operations such as global pooling layers at the end of the network, in which a higher weight indicates greater feature importance attributed to a given feature embedding in the set. In weakly-supervised algorithms for computational pathology, techniques such as attention-based multiple instance learning have been developed to saliently localize diagnostic and prognostic image regions in gigapixel pathology images, finding "needles in a haystack"<sup>258</sup>. Similarly in EMRs, visualization of self-attention weights in Transformer architectures have demonstrated that language models can learn relationships between clinical concept embeddings.

In combination with fairness and medicine, interpretability techniques can be used to audit failure modes of potential AI-SaMDs that would have disparate impact on under-served or under-represented subpopulations at deployment time. For instance, in model auditing of algorithms to predict credit limit, feature importances of demography data revealed surprisingly little attribution to male or female gender status<sup>259</sup>. On the COMPAS dataset, global shifts in interpretability via attribution-based methods were discovered following importance weighting<sup>97</sup>. In clinical scenarios, the recent discovery that found correlations site-specific staining variability and ethnicity in the TCGA was made via model auditing using attention-based interpretability on patch-based features<sup>29</sup>. In mortality prediction on EMR dataset, protected subgroups were found to have variable global feature importance, which revealed odd interactions such as different subsets of features being used for specific subgroups<sup>71</sup>. Though successful as an model auditing strategy in these examples, in the previous problem of unknown dataset shift of radiology images leaking self-reported race, saliency maps were used in performing model auditing but were unable to point towards explainable anatomic landmarks or image acquisition factors<sup>101</sup>. At the moment, the intersection of interpretability, fairness, and machine learning for health research remains quite a narrow, with only a few works examining the cross-section of how feature importances and interpretability shifts across protected subgroups<sup>71</sup>. As artificial intelligence continues to cross the

precipice into clinical workflows with calls to action on model auditing and interpretability gaining traction, FATML-centered research in healthcare will be center in refining FDA regulatory frameworks in AI-SaMDs.

## References

1. Adler, N. E., Glymour, M. M. & Fielding, J. Addressing social determinants of health and health inequalities. *Jama* **316**, 1641–1642 (2016).
2. Phelan, J. C. & Link, B. G. Is racism a fundamental cause of inequalities in health? *Annual Review of Sociology* **41**, 311–330 (2015).
3. Yehia, B. R. *et al.* Association of race with mortality among patients hospitalized with coronavirus disease 2019 (covid-19) at 92 us hospitals. *JAMA network open* **3**, e2018039–e2018039 (2020).
4. Lopez, L., Hart, L. H. & Katz, M. H. Racial and ethnic health disparities related to covid-19. *JAMA* **325**, 719–720 (2021).
5. Bonvicini, K. A. Lgbt healthcare disparities: What progress have we made? *Patient education and counseling* **100**, 2357–2361 (2017).
6. Yamada, T. *et al.* Access disparity and health inequality of the elderly: unmet needs and delayed healthcare. *International journal of environmental research and public health* **12**, 1745–1772 (2015).
7. Moy, E., Dayton, E. & Clancy, C. M. Compiling the evidence: The national healthcare disparities reports. *Health Affairs* **24**, 376–387 (2005).
8. Balsa, A. I., Seiler, N., McGuire, T. G. & Bloche, M. G. Clinical uncertainty and healthcare disparities. *American Journal of Law & Medicine* **29**, 203–219 (2003).
9. Marmot, M. Social determinants of health inequalities. *The lancet* **365**, 1099–1104 (2005).
10. Maness, S. B. *et al.* Social determinants of health and health disparities: Covid-19 exposures and mortality among african american people in the united states. *Public Health Reports* **136**, 18–22 (2021).
11. Seligman, H. K., Laraia, B. A. & Kushel, M. B. Food insecurity is associated with chronic disease among low-income nhanes participants. *The Journal of nutrition* **140**, 304–310 (2010).
12. Thun, M. J., Apicella, L. F. & Henley, S. J. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. *Jama* **284**, 706–712 (2000).
13. Ronsmans, C., Graham, W. J., steering group, L. M. S. S. *et al.* Maternal mortality: who, when, where, and why. *The lancet* **368**, 1189–1200 (2006).
14. MacDorman, M. F., Declercq, E. & Thoma, M. E. Trends in maternal mortality by socio-demographic characteristics and cause of death in 27 states and the district of columbia. *Obstetrics and gynecology* **129**, 811 (2017).
15. Matsuo, S., Yasuda, Y., IMAi, E. & Horio, M. Current status of estimated glomerular filtration rate (egfr) equations for asians and an approach to create a common egfr equation. *Nephrology* **15**, 45–48 (2010).
16. Delanaye, P. & Mariat, C. The applicability of egfr equations to different populations. *Nature Reviews Nephrology* **9**, 513–522 (2013).
17. Diao, J. A., Powe, N. R. & Manrai, A. K. Race-free equations for egfr: Comparing effects on ckd classification. *Journal of the American Society of Nephrology* **32**, 1868–1870 (2021).

18. van der Burgh, A. C., Hoorn, E. J. & Chaker, L. Removing race from kidney function estimates. *JAMA* **325**, 2018–2018 (2021).
19. Diao, J. A., Powe, N. R. & Manrai, A. K. Removing race from kidney function estimates—reply. *JAMA* **325**, 2018–2019 (2021).
20. Vyas, D. A., Eisenstein, L. G. & Jones, D. S. Hidden in plain sight—reconsidering the use of race correction in clinical algorithms (2020).
21. Buolamwini, J. & Gebru, T. Gender shades: Intersectional accuracy disparities in commercial gender classification. In *Conference on fairness, accountability and transparency*, 77–91 (PMLR, 2018).
22. Obermeyer, Z., Powers, B., Vogeli, C. & Mullainathan, S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* **366**, 447–453 (2019).
23. Pierson, E., Cutler, D. M., Leskovec, J., Mullainathan, S. & Obermeyer, Z. An algorithmic approach to reducing unexplained pain disparities in underserved populations. *Nature Medicine* **27**, 136–140 (2021).
24. Hooker, S. Moving beyond “algorithmic bias is a data problem”. *Patterns* **2**, 100241 (2021).
25. McCradden, M. D., Joshi, S., Mazwi, M. & Anderson, J. A. Ethical limitations of algorithmic fairness solutions in health care machine learning. *The Lancet Digital Health* **2**, e221–e223 (2020).
26. Mhasawade, V., Zhao, Y. & Chunara, R. Machine learning and algorithmic fairness in public and population health. *Nature Machine Intelligence* 1–8 (2021).
27. Currie, G. & Hawk, K. E. Ethical and legal challenges of artificial intelligence in nuclear medicine. In *Seminars in Nuclear Medicine* (Elsevier, 2020).
28. Chen, I. Y. *et al.* Ethical machine learning in healthcare. *Annual Review of Biomedical Data Science* **4** (2020).
29. Howard, F. M. *et al.* The impact of site-specific digital histology signatures on deep learning model accuracy and bias. *Nature communications* **12**, 1–13 (2021).
30. Seyyed-Kalantari, L., Liu, G., McDermott, M., Chen, I. Y. & Ghassemi, M. Chexclusion: Fairness gaps in deep chest x-ray classifiers. In *BIOCOMPUTING 2021: Proceedings of the Pacific Symposium*, 232–243 (World Scientific, 2020).
31. Food, U., Administration, D. *et al.* Proposed regulatory framework for modifications to artificial intelligence. *Machine Learning (AI/ML)-based Software as a Medical Device (SaMD)* **12** (2019).
32. Gaube, S. *et al.* Do as ai say: susceptibility in deployment of clinical decision-aids. *NPJ digital medicine* **4**, 1–8 (2021).
33. Corbett-Davies, S. & Goel, S. The measure and mismeasure of fairness: A critical review of fair machine learning. *arXiv preprint arXiv:1808.00023* (2018).
34. Barocas, S., Hardt, M. & Narayanan, A. Fairness in machine learning. *Nips tutorial* **1**, 2017 (2017).
35. Calders, T., Kamiran, F. & Pechenizkiy, M. Building classifiers with independency constraints. In *2009 IEEE International Conference on Data Mining Workshops*, 13–18 (IEEE, 2009).
36. Chen, J., Kallus, N., Mao, X., Svacha, G. & Udell, M. Fairness under unawareness: Assessing disparity when protected class is unobserved. In *Proceedings of the conference on fairness, accountability, and transparency*, 339–348 (2019).
37. Feller, A., Pierson, E., Corbett-Davies, S. & Goel, S. A computer program used for bail and sentencing decisions was labeled biased against blacks. it's actually not that clear. *The Washington Post* **17** (2016).

38. Kleinberg, J., Mullainathan, S. & Raghavan, M. Inherent Trade-Offs in the Fair Determination of Risk Scores. In *8th Innovations in Theoretical Computer Science Conference (ITCS 2017)*, vol. 67 of *Leibniz International Proceedings in Informatics (LIPIcs)*, 43:1–43:23 (Schloss Dagstuhl–Leibniz-Zentrum fuer Informatik, Dagstuhl, Germany, 2017). URL <http://drops.dagstuhl.de/opus/volltexte/2017/8156>.
39. Hardt, M., Price, E. & Srebro, N. Equality of opportunity in supervised learning. *Advances in neural information processing systems* **29**, 3315–3323 (2016).
40. Celis, L. E. & Keswani, V. Improved adversarial learning for fair classification. *arXiv preprint arXiv:1901.10443* (2019).
41. Kamiran, F. & Calders, T. Data preprocessing techniques for classification without discrimination. *Knowledge and Information Systems* **33**, 1–33 (2012).
42. Krasanakis, E., Spyromitros-Xioufis, E., Papadopoulos, S. & Kompatsiaris, Y. Adaptive sensitive reweighting to mitigate bias in fairness-aware classification. In *Proceedings of the 2018 World Wide Web Conference*, 853–862 (2018).
43. Jiang, H. & Nachum, O. Identifying and correcting label bias in machine learning. In *International Conference on Artificial Intelligence and Statistics*, 702–712 (PMLR, 2020).
44. Chai, X. *et al.* Unsupervised domain adaptation techniques based on auto-encoder for non-stationary eeg-based emotion recognition. *Computers in biology and medicine* **79**, 205–214 (2016).
45. Kamishima, T., Akaho, S., Asoh, H. & Sakuma, J. Fairness-aware classifier with prejudice remover regularizer. In *Joint European Conference on Machine Learning and Knowledge Discovery in Databases*, 35–50 (Springer, 2012).
46. Zafar, M. B., Valera, I., Rogriguez, M. G. & Gummadi, K. P. Fairness constraints: Mechanisms for fair classification. In *Artificial Intelligence and Statistics*, 962–970 (PMLR, 2017).
47. Goel, N., Yaghini, M. & Faltings, B. Non-discriminatory machine learning through convex fairness criteria. In *Thirty-Second AAAI Conference on Artificial Intelligence* (2018).
48. Agarwal, A., Beygelzimer, A., Dudík, M., Langford, J. & Wallach, H. A reductions approach to fair classification. In *International Conference on Machine Learning*, 60–69 (PMLR, 2018).
49. Pleiss, G., Raghavan, M., Wu, F., Kleinberg, J. & Weinberger, K. Q. On fairness and calibration. *arXiv preprint arXiv:1709.02012* (2017).
50. Chouldechova, A., Benavides-Prado, D., Fialko, O. & Vaithianathan, R. A case study of algorithm-assisted decision making in child maltreatment hotline screening decisions. In *Conference on Fairness, Accountability and Transparency*, 134–148 (PMLR, 2018).
51. Cheng, D. T. *et al.* Memorial sloan kettering-integrated mutation profiling of actionable cancer targets (msk-impact): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *The Journal of molecular diagnostics* **17**, 251–264 (2015).
52. Liu, J. *et al.* An integrated tcga pan-cancer clinical data resource to drive high-quality survival outcome analytics. *Cell* **173**, 400–416 (2018).
53. Sudlow, C. *et al.* Uk biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS medicine* **12**, e1001779 (2015).
54. Puyol-Anton, E. *et al.* Fairness in cardiac mr image analysis: An investigation of bias due to data imbalance in deep learning based segmentation. *arXiv preprint arXiv:2106.12387* (2021).

55. Shi, Y. *et al.* A prospective, molecular epidemiology study of egfr mutations in asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (pioneer). *Journal of thoracic oncology* **9**, 154–162 (2014).
56. McCarty, C. A. *et al.* The emerge network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. *BMC medical genomics* **4**, 1–11 (2011).
57. Gottesman, O. *et al.* The electronic medical records and genomics (emerge) network: past, present, and future. *Genetics in Medicine* **15**, 761–771 (2013).
58. Li, S., Cai, T. & Duan, R. Targeting underrepresented populations in precision medicine: A federated transfer learning approach. *arXiv preprint arXiv:2108.12112* (2021).
59. Foley, R. N., Wang, C. & Collins, A. J. Cardiovascular risk factor profiles and kidney function stage in the us general population: the nhanes iii study. In *Mayo Clinic Proceedings*, vol. 80, 1270–1277 (Elsevier, 2005).
60. Nevitt, M., Felson, D. & Lester, G. The osteoarthritis initiative. *Protocol for the cohort study* **1** (2006).
61. Vaughn, I. A., Terry, E. L., Bartley, E. J., Schaefer, N. & Fillingim, R. B. Racial-ethnic differences in osteoarthritis pain and disability: a meta-analysis. *The Journal of Pain* **20**, 629–644 (2019).
62. Rotemberg, V. *et al.* A patient-centric dataset of images and metadata for identifying melanomas using clinical context. *Scientific data* **8**, 1–8 (2021).
63. Kinyanjui, N. M. *et al.* Estimating skin tone and effects on classification performance in dermatology datasets. *arXiv preprint arXiv:1910.13268* (2019).
64. Kinyanjui, N. M. *et al.* Fairness of classifiers across skin tones in dermatology. In *International Conference on Medical Image Computing and Computer-Assisted Intervention*, 320–329 (Springer, 2020).
65. Chew, E. Y. *et al.* The age-related eye disease study 2 (areds2): study design and baseline characteristics (areds2 report number 1). *Ophthalmology* **119**, 2282–2289 (2012).
66. Joshi, N. & Burlina, P. Ai fairness via domain adaptation. *arXiv preprint arXiv:2104.01109* (2021).
67. Zhou, Y. *et al.* Radfusion: Benchmarking performance and fairness for multi-modal pulmonary embolism detection from ct and emr (2021).
68. Edwards, N. J. *et al.* The cptac data portal: a resource for cancer proteomics research. *Journal of proteome research* **14**, 2707–2713 (2015).
69. Johnson, A. E. *et al.* Mimic-iii, a freely accessible critical care database. *Scientific data* **3**, 1–9 (2016).
70. Boag, W., Suresh, H., Celi, L. A., Szolovits, P. & Ghassemi, M. Racial disparities and mistrust in end-of-life care. In *Machine Learning for Healthcare Conference*, 587–602 (PMLR, 2018).
71. Meng, C., Trinh, L., Xu, N. & Liu, Y. Mimic-if: Interpretability and fairness evaluation of deep learning models on mimic-iv dataset. *arXiv preprint arXiv:2102.06761* (2021).
72. Panigutti, C., Perotti, A., Panisson, A., Bajardi, P. & Pedreschi, D. Fairlens: Auditing black-box clinical decision support systems. *Information Processing & Management* **58**, 102657 (2021).
73. Irvin, J. *et al.* Chexpert: A large chest radiograph dataset with uncertainty labels and expert comparison. In *Proceedings of the AAAI conference on artificial intelligence*, vol. 33, 590–597 (2019).
74. Team, N. L. S. T. R. The national lung screening trial: overview and study design. *Radiology* **258**, 243–253 (2011).

75. Prosper, A. E. *et al.* Association of inclusion of more black individuals in lung cancer screening with reduced mortality. *JAMA Network Open* **4**, e2119629–e2119629 (2021).
76. Colak, E. *et al.* The rsna pulmonary embolism ct dataset. *Radiology: Artificial Intelligence* **3**, e200254 (2021).
77. Gertych, A., Zhang, A., Sayre, J., Pospiech-Kurkowska, S. & Huang, H. Bone age assessment of children using a digital hand atlas. *Computerized medical imaging and graphics* **31**, 322–331 (2007).
78. Sugiyama, M., Krauledat, M. & Müller, K.-R. Covariate shift adaptation by importance weighted cross validation. *Journal of Machine Learning Research* **8** (2007).
79. Buda, M., Maki, A. & Mazurowski, M. A. A systematic study of the class imbalance problem in convolutional neural networks. *Neural Networks* **106**, 249–259 (2018).
80. Goetz, M. *et al.* Dalsa: domain adaptation for supervised learning from sparsely annotated mr images. *IEEE transactions on medical imaging* **35**, 184–196 (2015).
81. Wachinger, C., Reuter, M., Initiative, A. D. N. *et al.* Domain adaptation for alzheimer’s disease diagnostics. *Neuroimage* **139**, 470–479 (2016).
82. Xue, C., Dou, Q., Shi, X., Chen, H. & Heng, P.-A. Robust learning at noisy labeled medical images: Applied to skin lesion classification. In *2019 IEEE 16th International Symposium on Biomedical Imaging (ISBI 2019)*, 1280–1283 (IEEE, 2019).
83. Globerson, A. & Roweis, S. Nightmare at test time: robust learning by feature deletion. In *Proceedings of the 23rd international conference on Machine learning*, 353–360 (2006).
84. Cortes, C., Mansour, Y. & Mohri, M. Learning bounds for importance weighting. In *Nips*, vol. 10, 442–450 (Citeseer, 2010).
85. Chen, I., Johansson, F. D. & Sontag, D. Why is my classifier discriminatory? *arXiv preprint arXiv:1805.12002* (2018).
86. Abernethy, J., Awasthi, P., Kleindessner, M., Morgenstern, J. & Zhang, J. Adaptive sampling to reduce disparate performance. *arXiv preprint arXiv:2006.06879* (2020).
87. Raji, I. D. & Buolamwini, J. Actionable auditing: Investigating the impact of publicly naming biased performance results of commercial ai products. In *Proceedings of the 2019 AAAI/ACM Conference on AI, Ethics, and Society*, 429–435 (2019).
88. Rolf, E., Worledge, T., Recht, B. & Jordan, M. I. Representation matters: Assessing the importance of subgroup allocations in training data. *arXiv preprint arXiv:2103.03399* (2021).
89. Iosifidis, V. & Ntoutsi, E. Dealing with bias via data augmentation in supervised learning scenarios. *Jo Bates Paul D. Clough Robert Jäschke* **24** (2018).
90. Vodrahalli, K., Li, K. & Malik, J. Are all training examples created equal? an empirical study. *arXiv preprint arXiv:1811.12569* (2018).
91. Barocas, S. & Selbst, A. D. Big data’s disparate impact. *Calif. L. Rev.* **104**, 671 (2016).
92. O’neil, C. *Weapons of math destruction: How big data increases inequality and threatens democracy* (Crown, 2016).
93. Celis, L. E., Deshpande, A., Kathuria, T. & Vishnoi, N. K. How to be fair and diverse? *arXiv preprint arXiv:1610.07183* (2016).
94. Lohr, S. L. Sampling: design and analysis: Nelson education (2009).

95. Chawla, N. V., Bowyer, K. W., Hall, L. O. & Kegelmeyer, W. P. Smote: synthetic minority over-sampling technique. *Journal of artificial intelligence research* **16**, 321–357 (2002).
96. Pukelsheim, F. *Optimal design of experiments* (SIAM, 2006).
97. Cesaro, J. & Cozman, F. G. Measuring unfairness through game-theoretic interpretability. *arXiv preprint arXiv:1910.05591* (2019).
98. Hu, W., Niu, G., Sato, I. & Sugiyama, M. Does distributionally robust supervised learning give robust classifiers? In *International Conference on Machine Learning*, 2029–2037 (PMLR, 2018).
99. Sagawa, S., Koh, P. W., Hashimoto, T. B. & Liang, P. Distributionally robust neural networks for group shifts: On the importance of regularization for worst-case generalization. *arXiv preprint arXiv:1911.08731* (2019).
100. Poplin, R. *et al.* Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nature Biomedical Engineering* **2**, 158–164 (2018).
101. Banerjee, I. *et al.* Reading race: Ai recognises patient’s racial identity in medical images. *arXiv preprint arXiv:2107.10356* (2021).
102. Kamishima, T., Akaho, S. & Sakuma, J. Fairness-aware learning through regularization approach. In *2011 IEEE 11th International Conference on Data Mining Workshops*, 643–650 (IEEE, 2011).
103. Zafar, M. B., Valera, I., Gomez Rodriguez, M. & Gummadi, K. P. Fairness beyond disparate treatment & disparate impact: Learning classification without disparate mistreatment. In *Proceedings of the 26th international conference on world wide web*, 1171–1180 (2017).
104. Kim, M. P., Reingold, O. & Rothblum, G. N. Fairness through computationally-bounded awareness. *arXiv preprint arXiv:1803.03239* (2018).
105. Goodfellow, I. *et al.* Generative adversarial nets. *Advances in neural information processing systems* **27** (2014).
106. Ganin, Y. & Lempitsky, V. Unsupervised domain adaptation by backpropagation. In *International conference on machine learning*, 1180–1189 (PMLR, 2015).
107. Zhao, H. & Gordon, G. Inherent tradeoffs in learning fair representations. *Advances in neural information processing systems* **32**, 15675–15685 (2019).
108. Rezaei, A., Fathony, R., Memarrast, O. & Ziebart, B. Fairness for robust log loss classification. In *Proceedings of the AAAI Conference on Artificial Intelligence*, vol. 34, 5511–5518 (2020).
109. Petrović, A., Nikolić, M., Radovanović, S., Delibašić, B. & Jovanović, M. Fair: Fair adversarial instance re-weighting. *arXiv preprint arXiv:2011.07495* (2020).
110. Sattigeri, P., Hoffman, S. C., Chenthamarakshan, V. & Varshney, K. R. Fairness gan: Generating datasets with fairness properties using a generative adversarial network. *IBM Journal of Research and Development* **63**, 3–1 (2019).
111. Xu, D., Yuan, S., Zhang, L. & Wu, X. Fairgan: Fairness-aware generative adversarial networks. In *2018 IEEE International Conference on Big Data (Big Data)*, 570–575 (IEEE, 2018).
112. Xu, H., Liu, X., Li, Y., Jain, A. & Tang, J. To be robust or to be fair: Towards fairness in adversarial training. In *International Conference on Machine Learning*, 11492–11501 (PMLR, 2021).
113. Wadsworth, C., Vera, F. & Piech, C. Achieving fairness through adversarial learning: an application to recidivism prediction. *arXiv preprint arXiv:1807.00199* (2018).

114. Adel, T., Valera, I., Ghahramani, Z. & Weller, A. One-network adversarial fairness. In *Proceedings of the AAAI Conference on Artificial Intelligence*, vol. 33, 2412–2420 (2019).
115. Zemel, R., Wu, Y., Swersky, K., Pitassi, T. & Dwork, C. Learning fair representations. In *International conference on machine learning*, 325–333 (PMLR, 2013).
116. Madras, D., Creager, E., Pitassi, T. & Zemel, R. Learning adversarially fair and transferable representations. In *International Conference on Machine Learning*, 3384–3393 (PMLR, 2018).
117. Liu, L. T., Simchowitz, M. & Hardt, M. The implicit fairness criterion of unconstrained learning. In *International Conference on Machine Learning*, 4051–4060 (PMLR, 2019).
118. Kearns, M., Neel, S., Roth, A. & Wu, Z. S. An empirical study of rich subgroup fairness for machine learning. In *Proceedings of the Conference on Fairness, Accountability, and Transparency*, 100–109 (2019).
119. Hébert-Johnson, U., Kim, M., Reingold, O. & Rothblum, G. Multicalibration: Calibration for the (computationally-identifiable) masses. In *International Conference on Machine Learning*, 1939–1948 (PMLR, 2018).
120. Vyas, D. A. *et al.* Challenging the use of race in the vaginal birth after cesarean section calculator. *Women's Health Issues* **29**, 201–204 (2019).
121. Curtis, J. R. *et al.* Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender. *Journal of general internal medicine* **24**, 956–962 (2009).
122. Heslin, K. C. *et al.* Trends in opioid-related inpatient stays shifted after the us transitioned to icd-10-cm diagnosis coding in 2015. *Medical care* **55**, 918–923 (2017).
123. Quiñonero-Candela, J., Sugiyama, M., Lawrence, N. D. & Schwaighofer, A. *Dataset shift in machine learning* (Mit Press, 2009).
124. Subbaswamy, A., Schulam, P. & Saria, S. Preventing failures due to dataset shift: Learning predictive models that transport. In *The 22nd International Conference on Artificial Intelligence and Statistics*, 3118–3127 (PMLR, 2019).
125. Subbaswamy, A. & Saria, S. From development to deployment: dataset shift, causality, and shift-stable models in health ai. *Biostatistics* **21**, 345–352 (2020).
126. Tedeschi, P. & Griffith, J. R. Classification of hospital patients as “surgical”: implications of the shift to icd-9-cm. *Medical care* **189**–192 (1984).
127. Castro, D. C., Walker, I. & Glocker, B. Causality matters in medical imaging. *Nature Communications* **11**, 1–10 (2020).
128. Kraft, S. A. *et al.* Beyond consent: building trusting relationships with diverse populations in precision medicine research. *The American Journal of Bioethics* **18**, 3–20 (2018).
129. West, K. M., Blacksher, E. & Burke, W. Genomics, health disparities, and missed opportunities for the nation’s research agenda. *Jama* **317**, 1831–1832 (2017).
130. Landry, L. G., Ali, N., Williams, D. R., Rehm, H. L. & Bonham, V. L. Lack of diversity in genomic databases is a barrier to translating precision medicine research into practice. *Health Affairs* **37**, 780–785 (2018).
131. Gao, J. *et al.* Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Science signaling* **6**, pl1–pl1 (2013).

132. Spratt, D. E. *et al.* Racial/ethnic disparities in genomic sequencing. *JAMA oncology* **2**, 1070–1074 (2016).
133. Zhang, G. *et al.* Characterization of frequently mutated cancer genes in chinese breast tumors: a comparison of chinese and tcga cohorts. *Annals of translational medicine* **7** (2019).
134. Duncan, L. *et al.* Analysis of polygenic risk score usage and performance in diverse human populations. *Nature communications* **10**, 1–9 (2019).
135. Lam, M. *et al.* Comparative genetic architectures of schizophrenia in east asian and european populations. *Nature genetics* **51**, 1670–1678 (2019).
136. Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature genetics* **51**, 584–591 (2019).
137. Manrai, A. K. *et al.* Genetic misdiagnoses and the potential for health disparities. *New England Journal of Medicine* **375**, 655–665 (2016).
138. Bejnordi, B. E. *et al.* Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. *Jama* **318**, 2199–2210 (2017).
139. Campanella, G. *et al.* Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nature medicine* **25**, 1301–1309 (2019).
140. Zavala, V. A. *et al.* Cancer health disparities in racial/ethnic minorities in the united states. *British journal of cancer* 1–18 (2020).
141. Zhang, W., Edwards, A., Flemington, E. K. & Zhang, K. Racial disparities in patient survival and tumor mutation burden, and the association between tumor mutation burden and cancer incidence rate. *Scientific reports* **7**, 1–9 (2017).
142. Ooi, S. L., Martinez, M. E. & Li, C. I. Disparities in breast cancer characteristics and outcomes by race/ethnicity. *Breast cancer research and treatment* **127**, 729–738 (2011).
143. Henderson, B. E., Lee, N. H., Seewaldt, V. & Shen, H. The influence of race and ethnicity on the biology of cancer. *Nature Reviews Cancer* **12**, 648–653 (2012).
144. Gamble, P. *et al.* Determining breast cancer biomarker status and associated morphological features using deep learning. *Communications Medicine* **1**, 1–12 (2021).
145. Kather, J. N. *et al.* Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nature medicine* **25**, 1054–1056 (2019).
146. Kather, J. N. *et al.* Pan-cancer image-based detection of clinically actionable genetic alterations. *Nature Cancer* **1**, 789–799 (2020).
147. Fu, Y. *et al.* Pan-cancer computational histopathology reveals mutations, tumor composition and prognosis. *Nature Cancer* **1**, 800–810 (2020).
148. Echle, A. *et al.* Deep learning in cancer pathology: a new generation of clinical biomarkers. *British journal of cancer* **124**, 686–696 (2021).
149. Shaban, M. T., Baur, C., Navab, N. & Albarqouni, S. Staingan: Stain style transfer for digital histological images. In *2019 IEEE 16th international symposium on biomedical imaging (Isbi 2019)*, 953–956 (IEEE, 2019).
150. Finlayson, S. G. *et al.* The clinician and dataset shift in artificial intelligence. *The New England Journal of Medicine* 283–286 (2020).

151. Guo, L. L. *et al.* Evaluation of domain generalization and adaptation on improving model robustness to temporal dataset shift in clinical medicine. *medRxiv* (2021).
152. Slack, D., Friedler, S. A. & Givental, E. Fairness warnings and fair-maml: learning fairly with minimal data. In *Proceedings of the 2020 Conference on Fairness, Accountability, and Transparency*, 200–209 (2020).
153. Dai, J., Fazelpour, S. & Lipton, Z. Fair machine learning under partial compliance. In *Proceedings of the 2021 AAAI/ACM Conference on AI, Ethics, and Society*, 55–65 (2021).
154. Heidari, H., Nanda, V. & Gummadi, K. P. On the long-term impact of algorithmic decision policies: Effort unfairness and feature segregation through social learning. *arXiv preprint arXiv:1903.01209* (2019).
155. Wen, M., Bastani, O. & Topcu, U. Algorithms for fairness in sequential decision making. In *International Conference on Artificial Intelligence and Statistics*, 1144–1152 (PMLR, 2021).
156. Board, A. E. Aaa statement on race. *American Anthropologist* **100**, 712–713 (1998).
157. Oni-Orisan, A., Mavura, Y., Banda, Y., Thornton, T. A. & Sebro, R. Embracing genetic diversity to improve black health (2021).
158. Calhoun, A. The pathophysiology of racial disparities. *New England Journal of Medicine* **384**, e78 (2021).
159. Sun, R. *et al.* Don't ignore genetic data from minority populations (2020).
160. Lannin, D. R. *et al.* Influence of socioeconomic and cultural factors on racial differences in late-stage presentation of breast cancer. *Jama* **279**, 1801–1807 (1998).
161. Bao, M. *et al.* It's compaslicated: The messy relationship between rai datasets and algorithmic fairness benchmarks. *arXiv preprint arXiv:2106.05498* (2021).
162. Hao, M. *et al.* Efficient and privacy-enhanced federated learning for industrial artificial intelligence. *IEEE Transactions on Industrial Informatics* **16**, 6532–6542 (2019).
163. Yang, Q., Liu, Y., Chen, T. & Tong, Y. Federated machine learning: Concept and applications. *ACM Transactions on Intelligent Systems and Technology (TIST)* **10**, 1–19 (2019).
164. Bonawitz, K. *et al.* Practical secure aggregation for privacy-preserving machine learning. In *proceedings of the 2017 ACM SIGSAC Conference on Computer and Communications Security*, 1175–1191 (2017).
165. Bonawitz, K. *et al.* Towards federated learning at scale: System design. *arXiv preprint arXiv:1902.01046* (2019).
166. Brisimi, T. S. *et al.* Federated learning of predictive models from federated electronic health records. *International journal of medical informatics* **112**, 59–67 (2018).
167. Huang, L. *et al.* Patient clustering improves efficiency of federated machine learning to predict mortality and hospital stay time using distributed electronic medical records. *Journal of biomedical informatics* **99**, 103291 (2019).
168. Xu, J. *et al.* Federated learning for healthcare informatics. *Journal of Healthcare Informatics Research* **5**, 1–19 (2021).
169. CHAKROBORTY, S., Patel, K. R. & Freytag, A. Beyond federated learning: fusion strategies for diabetic retinopathy screening algorithms trained from different device types. *Investigative Ophthalmology & Visual Science* **62**, 85–85 (2021).

170. Ju, C. *et al.* Federated transfer learning for eeg signal classification. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 3040–3045 (IEEE, 2020).
171. Li, W. *et al.* Privacy-preserving federated brain tumour segmentation. In *International Workshop on Machine Learning in Medical Imaging*, 133–141 (Springer, 2019).
172. Kaassis, G. *et al.* End-to-end privacy preserving deep learning on multi-institutional medical imaging. *Nature Machine Intelligence* **3**, 473–484 (2021).
173. Rieke, N. *et al.* The future of digital health with federated learning. *NPJ digital medicine* **3**, 1–7 (2020).
174. Sheller, M. J. *et al.* Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. *Scientific reports* **10**, 1–12 (2020).
175. Choudhury, O. *et al.* Differential privacy-enabled federated learning for sensitive health data. *arXiv preprint arXiv:1910.02578* (2019).
176. Kushida, C. A. *et al.* Strategies for de-identification and anonymization of electronic health record data for use in multicenter research studies. *Medical care* **50**, S82 (2012).
177. van der Haak, M. *et al.* Data security and protection in cross-institutional electronic patient records. *International journal of medical informatics* **70**, 117–130 (2003).
178. Veale, M. & Binns, R. Fairer machine learning in the real world: Mitigating discrimination without collecting sensitive data. *Big Data & Society* **4**, 2053951717743530 (2017).
179. Fiume, M. *et al.* Federated discovery and sharing of genomic data using beacons. *Nature biotechnology* **37**, 220–224 (2019).
180. Hernandez, J. B. *et al.* Privacy-first health research with federated learning. *medRxiv* (2020).
181. Duan, R., Boland, M. R., Moore, J. H. & Chen, Y. Odal: A one-shot distributed algorithm to perform logistic regressions on electronic health records data from multiple clinical sites. In *BIOCOMPUTING 2019: Proceedings of the Pacific Symposium*, 30–41 (World Scientific, 2018).
182. Sarma, K. V. *et al.* Federated learning improves site performance in multicenter deep learning without data sharing. *Journal of the American Medical Informatics Association* **28**, 1259–1264 (2021).
183. Silva, S. *et al.* Federated learning in distributed medical databases: Meta-analysis of large-scale subcortical brain data. In *2019 IEEE 16th international symposium on biomedical imaging (ISBI 2019)*, 270–274 (IEEE, 2019).
184. Roy, A. G., Siddiqui, S., Pölsterl, S., Navab, N. & Wachinger, C. Braintorrent: A peer-to-peer environment for decentralized federated learning. *arXiv preprint arXiv:1905.06731* (2019).
185. Lu, M. Y. *et al.* Federated learning for computational pathology on gigapixel whole slide images. *arXiv preprint arXiv:2009.10190* (2020).
186. Dou, Q. *et al.* Federated deep learning for detecting covid-19 lung abnormalities in ct: a privacy-preserving multinational validation study. *NPJ digital medicine* **4**, 1–11 (2021).
187. Yang, D. *et al.* Federated semi-supervised learning for covid region segmentation in chest ct using multi-national data from china, italy, japan. *Medical image analysis* **70**, 101992 (2021).
188. Vaid, A. *et al.* Federated learning of electronic health records to improve mortality prediction in hospitalized patients with covid-19: Machine learning approach. *JMIR medical informatics* **9**, e24207 (2021).
189. Mandl, K. D. *et al.* The genomics research and innovation network: creating an interoperable, federated, genomics learning system. *Genetics in Medicine* **22**, 371–380 (2020).

190. Cai, M. *et al.* A unified framework for cross-population trait prediction by leveraging the genetic correlation of polygenic traits. *The American Journal of Human Genetics* **108**, 632–655 (2021).
191. Liang, J., Hu, D. & Feng, J. Do we really need to access the source data? source hypothesis transfer for unsupervised domain adaptation. In *International Conference on Machine Learning*, 6028–6039 (PMLR, 2020).
192. Song, L., Ma, C., Zhang, G. & Zhang, Y. Privacy-preserving unsupervised domain adaptation in federated setting. *IEEE Access* **8**, 143233–143240 (2020).
193. Li, X. *et al.* Multi-site fmri analysis using privacy-preserving federated learning and domain adaptation: Abide results. *Medical Image Analysis* **65**, 101765 (2020).
194. Peterson, D., Kanani, P. & Marathe, V. J. Private federated learning with domain adaptation. *arXiv preprint arXiv:1912.06733* (2019).
195. Peng, X., Huang, Z., Zhu, Y. & Saenko, K. Federated adversarial domain adaptation. *arXiv preprint arXiv:1911.02054* (2019).
196. Yao, C.-H. *et al.* Federated multi-target domain adaptation. *arXiv preprint arXiv:2108.07792* (2021).
197. Zhao, Y. *et al.* Federated learning with non-iid data. *arXiv preprint arXiv:1806.00582* (2018).
198. Konečný, J. *et al.* Federated learning: Strategies for improving communication efficiency. *arXiv preprint arXiv:1610.05492* (2016).
199. Lin, Y., Han, S., Mao, H., Wang, Y. & Dally, W. J. Deep gradient compression: Reducing the communication bandwidth for distributed training. *arXiv preprint arXiv:1712.01887* (2017).
200. McMahan, B., Moore, E., Ramage, D., Hampson, S. & y Arcas, B. A. Communication-efficient learning of deep networks from decentralized data. In *Artificial intelligence and statistics*, 1273–1282 (PMLR, 2017).
201. Li, T. *et al.* Federated optimization in heterogeneous networks. *arXiv preprint arXiv:1812.06127* (2018).
202. Sattler, F., Wiedemann, S., Müller, K.-R. & Samek, W. Robust and communication-efficient federated learning from non-iid data. *IEEE transactions on neural networks and learning systems* **31**, 3400–3413 (2019).
203. Abay, A. *et al.* Mitigating bias in federated learning. *arXiv preprint arXiv:2012.02447* (2020).
204. McNamara, D., Ong, C. S. & Williamson, R. C. Costs and benefits of fair representation learning. In *Proceedings of the 2019 AAAI/ACM Conference on AI, Ethics, and Society*, 263–270 (2019).
205. Madaio, M. A., Stark, L., Wortman Vaughan, J. & Wallach, H. Co-designing checklists to understand organizational challenges and opportunities around fairness in ai. In *Proceedings of the 2020 CHI Conference on Human Factors in Computing Systems*, 1–14 (2020).
206. Awad, E. *et al.* The moral machine experiment. *Nature* **563**, 59–64 (2018).
207. Hong, J. *et al.* Federated adversarial debiasing for fair and transferable representations. In *Proceedings of the 27th ACM SIGKDD Conference on Knowledge Discovery & Data Mining*, 617–627 (2021).
208. Manica, A., Prugnolle, F. & Balloux, F. Geography is a better determinant of human genetic differentiation than ethnicity. *Human genetics* **118**, 366–371 (2005).
209. Bercea, C. I., Wiestler, B., Rueckert, D. & Albarqouni, S. Feddis: Disentangled federated learning for unsupervised brain pathology segmentation. *arXiv preprint arXiv:2103.03705* (2021).

210. Ke, J., Shen, Y. & Lu, Y. Style normalization in histology with federated learning. In *2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI)*, 953–956 (IEEE, 2021).
211. Pfohl, S. R., Dai, A. M. & Heller, K. Federated and differentially private learning for electronic health records. *arXiv preprint arXiv:1911.05861* (2019).
212. Xin, B. *et al.* Private fl-gan: Differential privacy synthetic data generation based on federated learning. In *ICASSP 2020-2020 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 2927–2931 (IEEE, 2020).
213. Rajotte, J.-F. *et al.* Reducing bias and increasing utility by federated generative modeling of medical images using a centralized adversary. *arXiv preprint arXiv:2101.07235* (2021).
214. Hadad, N., Wolf, L. & Shahar, M. A two-step disentanglement method. In *Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition*, 772–780 (2018).
215. Achille, A. & Soatto, S. Emergence of invariance and disentanglement in deep representations. *The Journal of Machine Learning Research* **19**, 1947–1980 (2018).
216. Chen, R. T., Li, X., Grosse, R. & Duvenaud, D. Isolating sources of disentanglement in variational autoencoders. *arXiv preprint arXiv:1802.04942* (2018).
217. Kim, H. & Mnih, A. Disentangling by factorising. In *International Conference on Machine Learning*, 2649–2658 (PMLR, 2018).
218. Higgins, I. *et al.* beta-vae: Learning basic visual concepts with a constrained variational framework (2016).
219. Ridgeway, K. & Mozer, M. C. Learning deep disentangled embeddings with the f-statistic loss. *arXiv preprint arXiv:1802.05312* (2018).
220. Eastwood, C. & Williams, C. K. A framework for the quantitative evaluation of disentangled representations. In *International Conference on Learning Representations* (2018).
221. Locatello, F. *et al.* Challenging common assumptions in the unsupervised learning of disentangled representations. In *international conference on machine learning*, 4114–4124 (PMLR, 2019).
222. Kumar, A., Sattigeri, P. & Balakrishnan, A. Variational inference of disentangled latent concepts from unlabeled observations. *arXiv preprint arXiv:1711.00848* (2017).
223. Sarhan, M. H., Eslami, A., Navab, N. & Albarqouni, S. Learning interpretable disentangled representations using adversarial vaes. In *Domain Adaptation and Representation Transfer and Medical Image Learning with Less Labels and Imperfect Data*, 37–44 (Springer, 2019).
224. Gyawali, P. K. *et al.* Learning to disentangle inter-subject anatomical variations in electrocardiographic data. *IEEE Transactions on Biomedical Engineering* (2021).
225. Bing, S., Fortuin, V. & Rätsch, G. On disentanglement in gaussian process variational autoencoders. *arXiv preprint arXiv:2102.05507* (2021).
226. Donahue, J. & Simonyan, K. Large scale adversarial representation learning. *arXiv preprint arXiv:1907.02544* (2019).
227. Chen, X. *et al.* Infogan: Interpretable representation learning by information maximizing generative adversarial nets. In *Proceedings of the 30th International Conference on Neural Information Processing Systems*, 2180–2188 (2016).
228. Nie, W. *et al.* Semi-supervised stylegan for disentanglement learning. In *International Conference on Machine Learning*, 7360–7369 (PMLR, 2020).

229. Jonnalagedda, P., Weinberg, B., Allen, J. & Bhanu, B. Feature disentanglement to aid imaging biomarker characterization for genetic mutations. In *Medical Imaging with Deep Learning*, 349–364 (PMLR, 2020).
230. Chartsias, A. *et al.* Disentangled representation learning in cardiac image analysis. *Medical image analysis* **58**, 101535 (2019).
231. Cisse, M. & Koyejo, S. Fairness and representation learning. *NeurIPS Invited Talk 2019* (2019).
232. Locatello, F. *et al.* On the fairness of disentangled representations. *arXiv preprint arXiv:1905.13662* (2019).
233. Li, P., Zhao, H. & Liu, H. Deep fair clustering for visual learning. In *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition*, 9070–9079 (2020).
234. Sarhan, M. H., Navab, N., Eslami, A. & Albarqouni, S. Fairness by learning orthogonal disentangled representations. In *European Conference on Computer Vision*, 746–761 (Springer, 2020).
235. Chen, T., Kornblith, S., Norouzi, M. & Hinton, G. A simple framework for contrastive learning of visual representations. In *International conference on machine learning*, 1597–1607 (PMLR, 2020).
236. Caron, M. *et al.* Emerging properties in self-supervised vision transformers. *arXiv preprint arXiv:2104.14294* (2021).
237. Simonyan, K., Vedaldi, A. & Zisserman, A. Deep inside convolutional networks: Visualising image classification models and saliency maps. *arXiv preprint arXiv:1312.6034* (2013).
238. Selvaraju, R. R. *et al.* Grad-cam: Visual explanations from deep networks via gradient-based localization. In *Proceedings of the IEEE international conference on computer vision*, 618–626 (2017).
239. Sayres, R. *et al.* Using a deep learning algorithm and integrated gradients explanation to assist grading for diabetic retinopathy. *Ophthalmology* **126**, 552–564 (2019).
240. Patro, B. N., Lunayach, M., Patel, S. & Namboodiri, V. P. U-cam: Visual explanation using uncertainty based class activation maps. In *Proceedings of the IEEE/CVF International Conference on Computer Vision*, 7444–7453 (2019).
241. Grewal, M., Srivastava, M. M., Kumar, P. & Varadarajan, S. Radnet: Radiologist level accuracy using deep learning for hemorrhage detection in ct scans. In *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*, 281–284 (IEEE, 2018).
242. Arun, N. T. *et al.* Assessing the validity of saliency maps for abnormality localization in medical imaging. *arXiv preprint arXiv:2006.00063* (2020).
243. Schlemper, J. *et al.* Attention-gated networks for improving ultrasound scan plane detection. *arXiv preprint arXiv:1804.05338* (2018).
244. Schlemper, J. *et al.* Attention gated networks: Learning to leverage salient regions in medical images. *Medical image analysis* **53**, 197–207 (2019).
245. Oktay, O. *et al.* Attention u-net: Learning where to look for the pancreas. *arXiv preprint arXiv:1804.03999* (2018).
246. Chen, R. J. *et al.* Pathomic fusion: an integrated framework for fusing histopathology and genomic features for cancer diagnosis and prognosis. *IEEE Transactions on Medical Imaging* (2020).
247. Chen, R. J. *et al.* Pan-cancer integrative histology-genomic analysis via interpretable multimodal deep learning. *arXiv preprint arXiv:2108.02278* (2021).
248. Sharma, D. *et al.* Deep interpretability for gwas. *arXiv preprint arXiv:2007.01516* (2020).

249. Hickey, J. M., Di Stefano, P. G. & Vasileiou, V. Fairness by explicability and adversarial shap learning. *arXiv preprint arXiv:2003.05330* (2020).
250. Lundberg, S. M. & Lee, S.-I. A unified approach to interpreting model predictions. In *Proceedings of the 31st international conference on neural information processing systems*, 4768–4777 (2017).
251. Sundararajan, M., Taly, A. & Yan, Q. Axiomatic attribution for deep networks. In *International Conference on Machine Learning*, 3319–3328 (PMLR, 2017).
252. Janizek, J. D., Sturmels, P. & Lee, S.-I. Explaining explanations: Axiomatic feature interactions for deep networks. *Journal of Machine Learning Research* **22**, 1–54 (2021).
253. Tsang, M., Rambhatla, S. & Liu, Y. How does this interaction affect me? interpretable attribution for feature interactions. *arXiv preprint arXiv:2006.10965* (2020).
254. Zeiler, M. D. & Fergus, R. Visualizing and understanding convolutional networks. In *European conference on computer vision*, 818–833 (Springer, 2014).
255. Kindermans, P.-J. *et al.* The (un) reliability of saliency methods. In *Explainable AI: Interpreting, Explaining and Visualizing Deep Learning*, 267–280 (Springer, 2019).
256. Hooker, S., Erhan, D., Kindermans, P.-J. & Kim, B. A benchmark for interpretability methods in deep neural networks. *arXiv preprint arXiv:1806.10758* (2018).
257. Ilse, M., Tomczak, J. & Welling, M. Attention-based deep multiple instance learning. In *International conference on machine learning*, 2127–2136 (PMLR, 2018).
258. Lu, M. Y. *et al.* Data-efficient and weakly supervised computational pathology on whole-slide images. *Nature Biomedical Engineering* 1–16 (2021).
259. Adebayo, J. & Kagal, L. Iterative orthogonal feature projection for diagnosing bias in black-box models. *arXiv preprint arXiv:1611.04967* (2016).