

# Advancing Medical Imaging Informatics by Deep Learning-Based Domain Adaptation

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## Summary

**Introduction:** There has been a rapid development of deep learning (DL) models for medical imaging. However, DL requires a large labeled dataset for training the models. Getting large-scale labeled data remains a challenge, and multi-center datasets suffer from heterogeneity due to patient diversity and varying imaging protocols. Domain adaptation (DA) has been developed to transfer the knowledge from a labeled data domain to a related but unlabeled domain in either image space or feature space. DA is a type of transfer learning (TL) that can improve the performance of models when applied to multiple different datasets.

**Objective:** In this survey, we review the state-of-the-art DL-based DA methods for medical imaging. We aim to summarize recent advances, highlighting the motivation, challenges, and opportunities, and to discuss promising directions for future work in DA for medical imaging.

**Methods:** We surveyed peer-reviewed publications from leading biomedical journals and conferences between 2017-2020, that reported the use of DA in medical imaging applications, grouping them by methodology, image modality, and learning scenarios.

**Results:** We mainly focused on pathology and radiology as application areas. Among various DA approaches, we discussed domain transformation (DT) and latent feature-space transformation (LFST). We highlighted the role of unsupervised DA in image segmentation and described opportunities for future development.

**Conclusion:** DA has emerged as a promising solution to deal with the lack of annotated training data. Using adversarial techniques, unsupervised DA has achieved good performance, especially for segmentation tasks. Opportunities include domain transferability, multi-modal DA, and applications that benefit from synthetic data.

## Keywords

Medical Imaging Informatics, deep learning, domain adaptation, domain transformation, latent feature space transformation, precision medicine

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## 1 Introduction

Medical imaging informatics utilizes digital imaging processing and machine learning (ML) to improve the efficiency, accuracy, and reliability of imaging-based diagnosis [1]. During the past few years, medical imaging informatics has made remarkable progress due to the increasing availability of data and the rapid development of deep learning (DL) techniques [2]. However, fundamental challenges hinder the effective deployment of deep learning models to clinical settings. Annotated medical datasets are limited due to the tedious labeling process [2] and are not easily shared due to privacy concerns [3, 4]. While multicenter datasets can increase the amount of annotated data, these datasets suffer from heterogeneity due to varying hospital procedures and diverse patient populations [5, 6]. Due to a distribution shift (also known as domain-shift) between the available training dataset and the dataset encountered in clinical practice, pre-trained models trained by one dataset may fail for another dataset.

### 1.1 What is Transfer Learning and Domain Adaptation

Transfer learning (TL) [7] is a technique that applies knowledge learned from one domain and one task to another related domain and/or another task, when there is insufficient labeled data for traditional supervised learning. For medical imaging, a domain usually refers to images or features, while the task refers to segmentation, clas-

sification, etc. Mathematically,  $X$  and  $Y$  being random variables, where  $X$  is  $d$ -dimensional feature space with marginal probability distribution  $p(X)$  and  $Y$  is a labeled vector with conditional probability distribution  $p(Y|X)$ , we use  $D = \{X, p(X)\}$  to represent domain and  $T = \{Y, \hat{p}(Y|X)\}$  to represent task, where  $\hat{p}$  is learnt using a function (e.g. neural network). If both source ( $D_S$ ) and target domains ( $D_T$ ) are similar, *i.e.*,  $D_S \sim D_T$ , then  $D_S$  and  $D_T$  can use the same ML model for similar tasks ( $T_S \sim T_T$ ). However, if  $D_S \neq D_T$  or  $T_S \neq T_T$ , the ML model trained on the source domain might have decreased performance on the target domain ( $D_T$ ). TL can be categorized into three types based on the relationships between domains and/or tasks:

1. Inductive TL requires some labeled data. While the two domains may or may not differ ( $D_S \sim D_T$  or  $D_S \neq D_T$ ), the target and source tasks are different ( $T_S \neq T_T$ ), for *e.g.* 3D organ reconstruction across multiple anatomies;
2. Transductive TL requires labeled source data and unlabeled target data with related domains ( $D_S \sim D_T$ ) and same tasks ( $T_S = T_T$ ), while the marginal probability distributions differ ( $p(X_S) \neq p(X_T)$ ), for *e.g.* lung tumor detection across X-Ray and computed tomography images;
3. Unsupervised TL does not require labeled data in any domain and has different tasks ( $T_S \neq T_T$ ), for *e.g.*, classifying cancer for different anatomies using unlabeled histology images.

Domain Adaptation (DA) is a transductive TL approach that aims to transfer knowledge across domains by learning domain-invariant

transformations, which align the domain distributions (see Figure 1-b). DA assumes that the source data is labeled, while the target domain can be (a) fully labeled data (*i.e.*, supervised setting); (b) a small set of labeled data (*i.e.*, semi-supervised setting); or (c) completely unlabeled data (*i.e.*, unsupervised setting).

## 1.2 Using Domain Adaptation to Improve Model Training in Medical Imaging

In biomedical imaging, due to the existence of multi-modality imaging (*e.g.*, magnetic resonance imaging (MRI) and positron emission tomography (PET)), DA has advantages over conventional semi-supervised learning or unsupervised learning. Cross-modal DA transfers labels between distinct, but somewhat related, image modalities (*e.g.*, MRI and computed tomography (CT)). Single-modality DA adapts different image distributions within the same modality [8] (Figure 2).

### 1.2.1 Challenge of Limited Training Data

Developing accurate DL models requires large scale training data covering a wide range of input variations. However, in biomedical imaging, due to concerns over patient privacy [3,4] and lack of manual annotation of images by clinical experts [9], few well-labeled datasets are available for training. This situation is worse for rare diseases, where a low number of positive cases lead to significantly unbalanced datasets [10].

DA can mitigate the lack of well-annotated data by augmenting target domain data, either by generating synthetic labeled images from source images or aligning source and target image features and training a task network on them [11, 12, 112]. For example, MRI achieves higher resolution for soft tissue imaging compared to CT [13]. As such, MRI is preferred for neuroimaging, and brain MRI annotations are easily accessible. On the other hand, CT imaging is fast and less expensive and may be preferred in trauma situations [14]. Thus, through DA, annotated MRI scans from historical subjects can be combined with CT

to reduce the number of image acquisitions needed. As another example, Hematoxylin and Eosin (H&E) stained images are widely available, while immunohistochemistry (IHC) images, which clearly highlight nuclei via specific biomarkers [15], are not. DA methods can translate multi-stained H&E-stained images to the IHC domain, making nuclei detection easier [16].

### 1.2.2 Challenge of Dataset Variations

To train robust DL models, many studies rely on images aggregated from multiple institutes such as NCI/NIH The Cancer Genome Atlas (TCGA) [17] and Stanford's large chest radiograph dataset, CheXpert [18]. The data in these repositories are heterogeneous due to varying hospital processes (image acquisition platforms or data preparation protocols), different demographics of patient populations (ethnicity, gender, age), or different pathological conditions [5]. Specifically, pathology images have stain variations [19] while MRIs are susceptible to varying magnetic fields and contrast agents [20]. Such intra- or in-

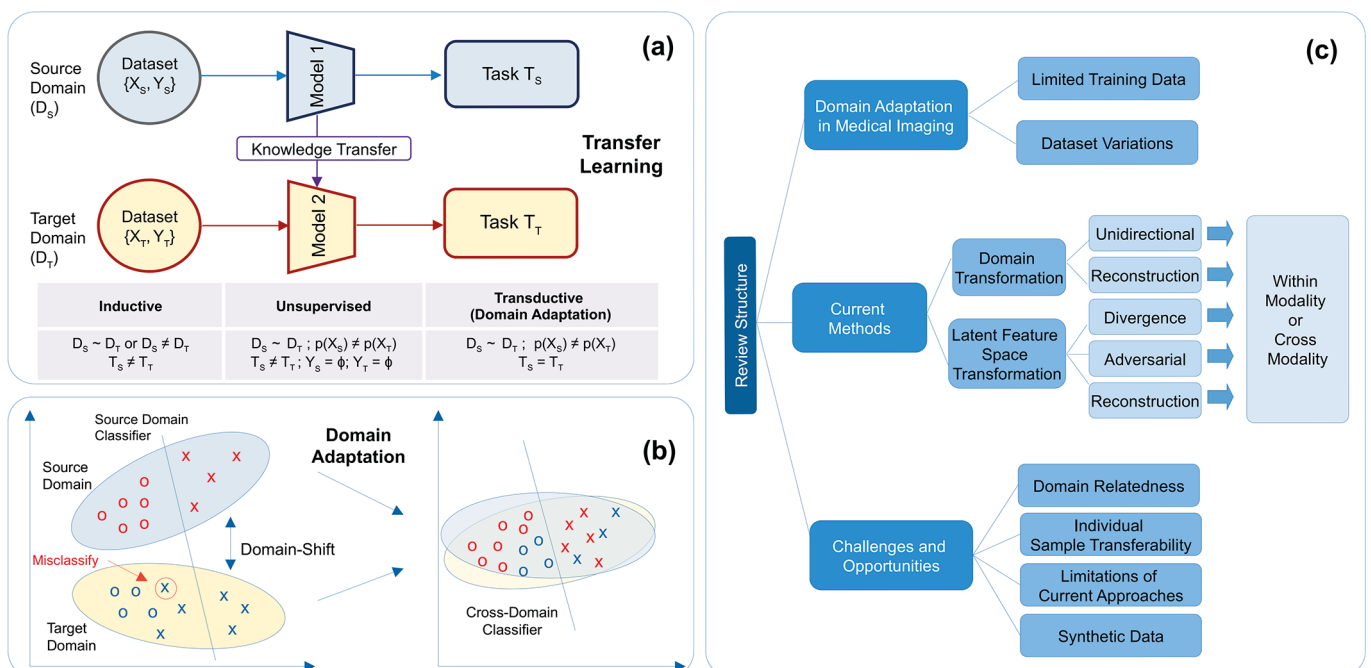
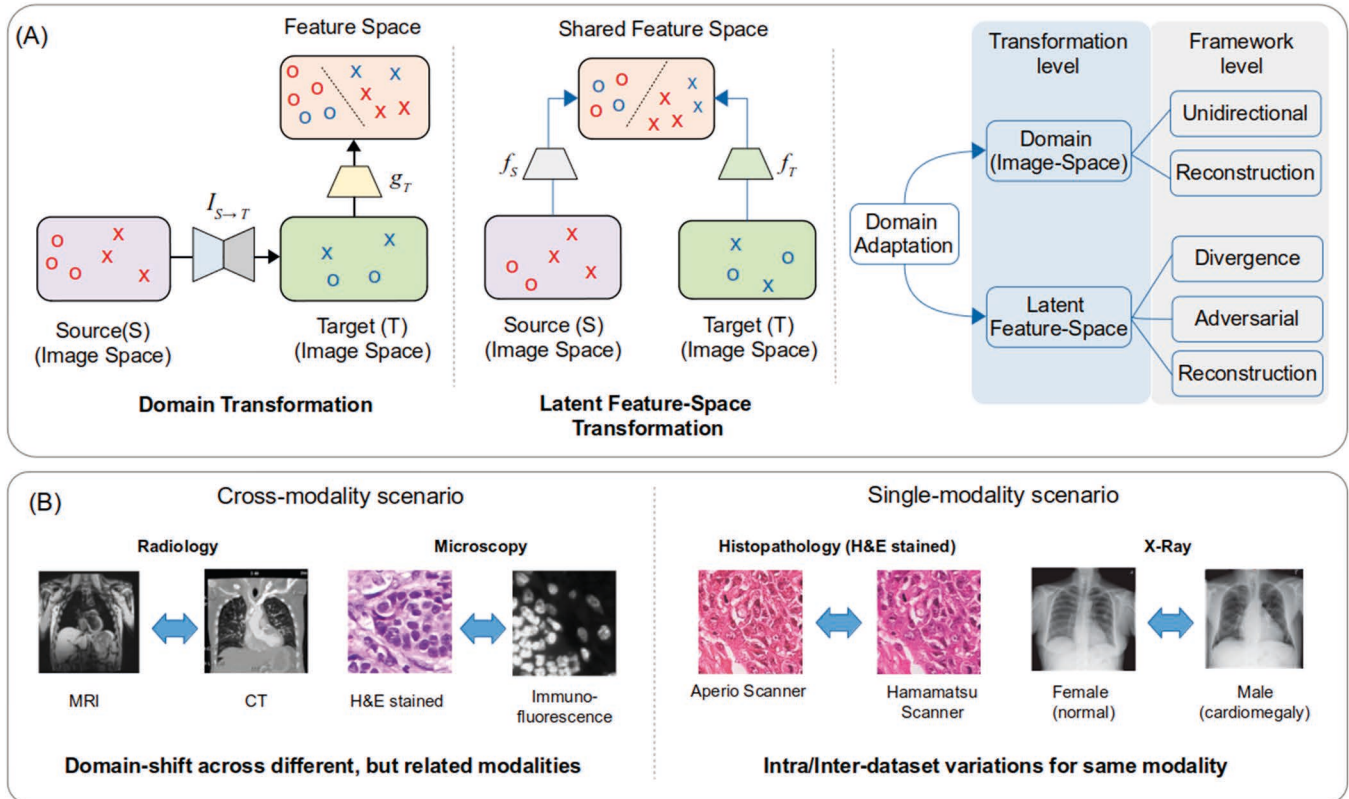


Fig. 1 a) Transfer learning (TL) and its different types; b) Overview of domain adaptation; c) Organization of this survey paper.



**Fig. 2** a) Summary of domain adaptation methodologies employed in medical imaging; b) Different scenarios encountered in cross-modality [16, 28] and single-modality [25, 29] domain adaptation.

ter-dataset variations cause the training and test dataset to have different distributions, resulting in a domain-shift which impacts model generalization [21, 22]. Diversifying the training data by creating larger datasets is a possible solution, but recent medical imaging studies [21, 23, 24] have shown that it does not guarantee improved generalization. DA methods try to minimize the dataset variation, while retaining the distinguishing aspects for task classifier, and have been shown to generalize well in image segmentation tasks for multiple modalities [25-27].

The organization of the survey paper is illustrated in Figure 1-c. Section 2 introduces our survey methodology in identifying and selecting relevant medical imaging studies. Section 3 presents various DL-based frameworks in the DA literature and the current best practices for medical imaging. Section 4 summarizes the current DA challenges and future opportunities.

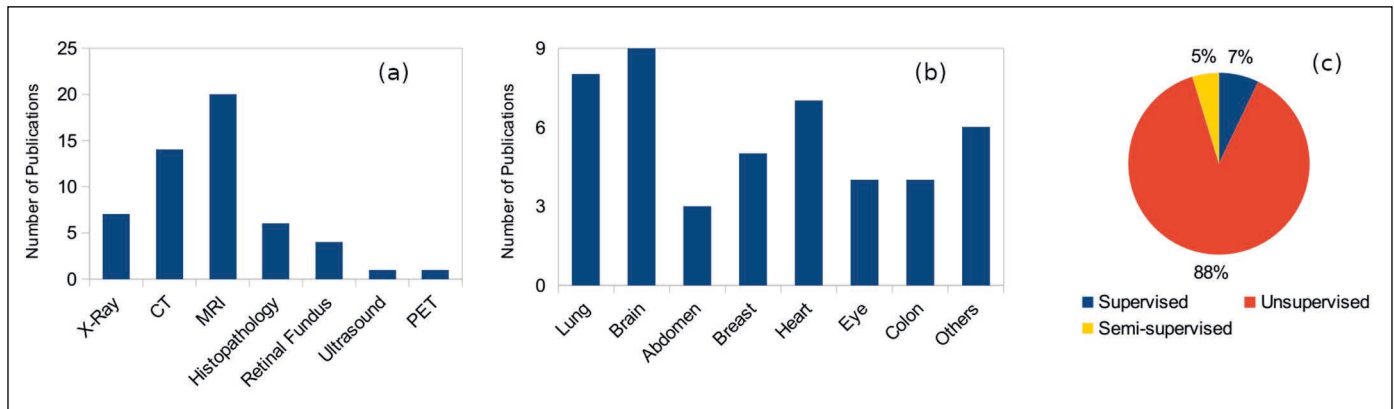
## 2 Materials and Methods

In this survey, we examined publications between 2017-2020. We considered the proceedings of leading peer-reviewed journals and conferences, including IEEE Transactions on Medical Imaging, the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), Medical Image Analysis (Elsevier), IEEE International Symposium on Biomedical Imaging (ISBI), Conference on Computer Vision and Pattern Recognition (CVPR), Association for the Advancement of Artificial Intelligence (AAAI), and the International Conference on Medical Imaging with Deep Learning (MIDL). Additionally, we identified a few relevant works from arXiv and PubMed, which were not found in review proceedings. Our search keywords included 'Domain Adaptation', 'Transfer Learning', 'Cross Modality', 'Multimodal' and 'Medical

Image Adaptation', and 'Medical Images'. We found that radiology and pathology were the most common application areas (characteristics of our results are illustrated in Figure 3-a and Figure 3-c). Cross-modality segmentation is observed more extensively in radiology compared to other areas. MRI, CT, and PET maintain better relative morphological-consistency of organs and provide complementary information for disease detection [30]. On the other hand, histopathology with smaller objects, such as nuclei, are prone to artifacts during cross-modal translation [31].

## 3 Deep Learning-based Domain Adaptation

DL-based DA is achieved using various representation learning strategies such as aligning the domain distributions, learning



**Fig. 3** Categorization of medical imaging DA publications as per a) imaging modality; b) anatomy; c) learning scenarios

a mapping between domains, separating normalization statistics, and ensemble-based approaches [32-34]. As shown in Figure 2-a, there are two families of DA approaches for medical imaging: (a) Domain Transformation (DT-DA) translates images from one domain to the other domain, so that the obtained models can be directly applied to all images, and (b) Latent Feature Space Transformation (LFST-DA) aligns images from both domains in a common hidden feature space to train the task model on top of the hidden features. These two approaches can work together to improve adaptation performance by preserving finer semantic details [35,36]. We have summarized the application of these DA methods in medical imaging in Table 1.

### 3.1 Domain Transformation in Domain Adaptation

DT-DA translates images from one domain to another domain (i.e., image-to-image translation [37]). Such translation is typically done using generative models (e.g., generative adversarial networks (GANs)) [38], which achieve pixel-level mapping by learning the translation at a semantic level. The translation direction is usually decided by the relative ease of translation and modeling in a modality [39]. For example, Dou *et al.*, [36] observed lower performance in adapting CT to MRI for cardiac images, since cardiac MRI is more challenging to

segment. The task networks are trained independently or jointly, with the image-translation network, using the labeled source images [35]. DT-DA performs alignment in the image space instead of the latent feature space, leading to better interpretability through visual inspection of synthesized images [40], enforcing semantic consistency, and preserving low-level appearance aspects using shape-consistency [41] and structural-similarity constraints [42].

#### 3.1.1 Unidirectional Translation

Unidirectional translation maps images from the source domain to the target domain or vice versa using GANs (e.g., vanilla GAN and conditional GAN (cGAN)) [43]. Compared with vanilla GAN, cGAN conditions the training of the generator and discriminator on extra information such as the class label. Yoo *et al.*, [44] proposed pixel-level domain transfer using cGAN with a domain discriminator. Liu and Tuzel [45] utilized GANs coupled with shared weights to generate paired synthetic source and target images sharing high-level abstraction. Bousmalis *et al.*, [40] leveraged cGAN with the content-similarity loss to generate realistic target images and jointly trained the GAN discriminator with the task network.

Unidirectional translation has been applied to remove dataset variations. For example, Bentaieb *et al.*, [29] designed a stain normalization approach, using a task conditional GAN to translate H&E images to a reference stain. Madani *et al.*, [46]

proposed a semi-supervised approach for cardiac abnormality classification using GAN discriminator for abnormality classification in minimally labeled X-ray images, and showed that the adversarial loss could reduce domain overfitting. Mahmood *et al.*, [39] translated real endoscopy images to graphically-rendered synthetic colon images with ground-truth annotations, for depth-estimation during surgical navigation. Unidirectional translation has also been applied to cross-modality scenario. For instance, Zhao *et al.*, [47] proposed a modified U-Net to translate paired brain CT to MRI.

#### 3.1.2 Bidirectional Translation

Bidirectional image translation (also known as reconstruction-based DT) leverages two GANs, constraining the mapping space by enforcing semantic-consistency between the original and reconstructed images. CycleGAN, by Zhu *et al.* [48], is one of the most popular architectures for bidirectional translation. CycleGAN utilizes cycle-consistency to constrain the translation mapping and improve the quality of generated images. CycleGAN has been expanded to handle larger domain shifts with semantic-consistency loss functions (CyCADA [35]), multi-domain translation (StarGAN [49]), and translation between two domains with multi-modal conditional distributions (MUNIT [50]). In supervised learning, bidirectional translation expands the training data to make the segmentation task model



robust. The translation and segmentation network can be trained either independently (two stages) or jointly. Zhang *et al.*, [51] presented a one-stage framework with an additional shape-consistency loss in CycleGAN to achieve better segmentation masks and lower failures. Chartsias *et al.*, [11] used a two-stage framework to segment MRI images using CT images. Cai *et al.*, [52] combined segmentation loss on generated images as an additional shape constraint for 3D translation and leveraged MRI for pancreas segmentation in CT images. In the unsupervised setting, image translation is used to create labeled data for the target domain. Huo *et al.*, [12] proposed a joint optimization approach for the synthesis and segmentation of CT images using labeled MRI. Their framework achieved comparable performance in comparison to the fully labeled case.

There are a few observations about GANs: (a) CycleGAN does not guarantee consistent translation of minor anatomical structures and boundaries [53], and thus needs additional constraints like gradient [53] and shape consistency [51]. For instance, Jiang *et al.*, [54] incorporated tumor-shape and feature-based losses to preserve tumors while translating CT data to MRI data; (b) Attention networks can account for varying transferability of different image regions [55]. For instance, Liu *et al.*, [56] proposed a novel attention-based U-Net [57] as a GAN generator to translate hard-to-generate textured regions from MRI to CT. For alternate scenarios such as 3D-2D, paired images, or semi-supervised DA-DT, Zhang *et al.*, [51] segmented X-ray images by using synthetic X-ray images created from accessible 3D CT annotations. Nguyen *et al.*, [58] used semi-supervised DA with paired CT images to constrain CycleGAN to generate more realistic images. Pan *et al.*, [30] leveraged MRI to generate missing PET images for patients for Alzheimer's disease diagnosis. Chen *et al.*, [59] proposed state-of-the-art unsupervised segmentation method using bidirectional DA-DT between MRI and CT, combining CycleGAN with shared feature encoder layers between domains. Their method resembled CyCADA [41] and showed the efficacy of combining DT with feature-based alignment; (c) DA-DT can be used for single-modality medical imaging. Chen *et al.*, [28] leveraged

a CycleGAN with semantic-aware adversarial loss to perform lung segmentation across different chest X-ray datasets.

## 3.2 Latent Feature Space Transformation in Domain Adaptation

Unlike the image-to-image translation in DT-DA, the LFST-DA transforms the source domain and target domain images to a shared latent feature space to learn a domain-invariant feature representation. The goal is to minimize domain-specific information while preserving the task-related information. The LFST-DA can be trained in an unsupervised fashion to obtain a domain-invariant representation, or in a concurrent manner where the representation network and the task network (*e.g.*, image classification network) are trained simultaneously to improve the performance. LFST-DA is used in three basic implementations: divergence minimization [60-64], adversarial training [65-68], and cross-domain reconstruction [69,70]. Compared to DT-DA, LSFT-DA is more computationally efficient because it focuses on translating relevant information only instead of the complete image [34]. Also, feature-based domain alignment outperforms DT-DA by preserving task-critical features [35].

### 3.2.1 Divergence Minimization

A simple approach to learn domain-invariant features and remove distribution-shift is to minimize some divergence criterion between source and target data distributions. Common choices include maximum mean discrepancy (MMD) [60], correlation alignment (CORAL) [61, 63], contrastive domain discrepancy (CDD) [64], and Wasserstein distance [62]. MMD, CORAL, and Wasserstein distances are class-agnostic divergence metrics and do not discriminate class labels when aligning samples. CDD-based DA aligns samples based on their labels, by minimizing the intra-class discrepancy and maximizing the inter-class discrepancy. MMD and CORAL are two of the most utilized divergence metrics that match the first-order moment (mean) and the second-order moment (covariance) of distributions. However, the represented hidden

features can be complicated in the real world and may not be fully characterized by mean and covariance. Wasserstein distance aligns feature distributions between domains via optimal transport theory. Compared to the adversarial-based approaches, divergence-based DA has not been as widely explored in medical imaging. For cross-modality DA, Zhu *et al.*, [71] utilized maximum mean discrepancy to map MR and PET images to a common space to mitigate missing data. Several works have used same-modality DA to mitigate dataset variations in X-ray [72], retinal fundus [73], and electron microscopy images [74].

### 3.2.2 Adversarial Training

Instead of minimizing a divergence metric, adversarial methods train a discriminator, typically a separate network, in an adversarial fashion against the feature encoder network. The goal of the feature network is to learn a latent representation such that the discriminator is unable to identify the input sample domain from the representation. For medical imaging, feature-based adversarial domain adaptation has been widely utilized for various applications. For example, in cross-modality adaptation, Zhang *et al.*, [75] applied a domain discriminator to adapt models trained for pathology images to microscopy images. LSFT-DA is also used for single-modality adaptation to overcome dataset variations in pathology images, MR images, and ultrasound images. For example, Lafarge *et al.*, [76] have utilized a domain discriminator to mitigate the color variations of histopathology images for mitosis detection in breast cancer. Kamnitsas *et al.*, [77] have applied a domain discriminator to MR images from different scanners and imaging protocols to improve the brain lesion segmentation performance.

### 3.2.3 Reconstruction-based Adaptation

The reconstruction-based adaptation maximizes the inter-domain similarity by encoding images from each domain to reconstruct images in the other domain. The reconstruction network (decoder) performs feature alignment by recreating the feature extractor's input while the feature extractor (encoder) transforms input image into latent representation. Ghifary *et al.*, [70] proposed

DRCN for object detection, using only target domain data reconstruction while Bousmalis *et al.*, [69] proposed a domain separation network that extracts image representations in two subspaces: the private domain features and the shared-domain features, the latter being used to reconstruct input image. For medical imaging, reconstruction-based methods are less developed and are usually combined with adversarial learning. For same-modality adaptation, Oliveira *et al.*, [80] have combined image-to-image translation with a feature-based discriminator to mitigate the variations in X-ray images and improve segmentation performance. For cross-modality adaptation, Ouyang *et al.*, [81] combined variational autoencoder (VAE) with adversarial training to adapt MR to CT scans.

## 4 Challenges and Opportunities

### 4.1 Domain Selection and Direction of Domain Adaptation

Selecting related domains for effective knowledge transfer is an open-research area in ML. In medical imaging, domains are often selected based on the type of imaging technique (*e.g.*, radiology), anatomy, availability of labeled data, and whether the modalities are complementary for the underlying task [30]. Regarding whether DA could be performed symmetrically across domains, the potential information loss in a particular direction is critical for assessing task performance. For example, for unsupervised DA from CT to MRI, reverse DA may sometimes be needed to preserve tumors [54]. For supervised DA between multiple H&E stained images, Tellez *et al.*, [82] showed that mitosis-detection and cancer tissue classification in a particular color space leads to higher accuracy. Typically, to assess domain relationship and DA direction, it is necessary to use (a) large-scale empirical studies such as [6,58] exploring bi-directional DA across multiple datasets, (b) a representation-shift metric [24] to roughly quantify the risk of applying learned-representations from a particular domain to a new domain, or (c) multi-source DA [83], which automatically explores latent source domains in multi-

source datasets and quantifies the membership of each target sample. However, such experimentation requires extensive benchmarking studies that are lacking in medical imaging.

### 4.2 Transferability of Individual Samples

Most DA studies for medical imaging assume that all samples are equally transferable across two domains. Thus, they focus on globally aligning domain distributions. However, the ability to transfer (or align) varies across clinical samples because of: (a) intra-domain variations (*e.g.*, in multi-modal DA between MRI and CT, each modality can have contrast variations) [75]; (b) noisy annotations due to human subjectivity; (c) target label space being a subset of source label space [84]; and (d) varying transferability among different image regions [55] (*e.g.*, tumors are difficult to translate and could be missed during CT to MRI image-translation [54]). Some samples in the source domain may be less useful and can lead to negative transferring [84], which adversely impacts DA. Selecting relevant samples or reducing the impact of outlier samples using transferability frameworks is a potential solution. Some strategies include weighting samples based on classifier discrepancy [85], down-weighting outlier classes using the classification probability for target data [86], leveraging open-set based optimization [87], and leveraging an attention mechanism [55] to focus on hard-to-transfer samples or using a noise co-adaptation layer [88]. Recent medical imaging studies have explored sample selection and transferability assessment using reverse classification accuracy [89], attention-based U-Net [56], and transferable semantic representations [84].

### 4.3 Limitations of Domain Adaptation in Medical Imaging

For medical imaging, most DL-based DA uses adversarial methods, primarily GAN for unsupervised DA. Adversarial methods are prone to errors because the discriminator can be confused, and there is no guarantee that the domain distributions are sufficiently similar [90]. Moreover, the generator in GAN is prone

to “hallucinating” content to convince the discriminator that data belongs to the target distribution [91]. As such, CycleGAN could be trained to synthesize tumors in images of healthy patients. Beyond applying consistency constraints during image translation, artifacts which are not directly visible in synthesized images, are also important for consideration. For example, CycleGANs incorporate high-frequency information in the intermediate representation used by the second generator to translate the image back to the source domain [92]. This high frequency information can interfere with downstream tasks.

DT-DA approaches require translating the entire image, increasing the complexity of the models for large-sized medical images like whole slide images. Few studies [28, 36] have compared adversarial DA methods for MRI-CT translation. However, a comprehensive comparison of various feature-based DA approaches is lacking. Future studies could explore combining DT-DA and LFST-DA approaches [59]. Moreover, current frameworks typically focus on source-target domain pair, while many tasks, such as stain normalization in histopathology images, can be multi-domain [93].

### 4.4 Leveraging Synthetic Data

DA for medical imaging can be applied in relatively under-explored applications such as single-view 3D reconstruction [94] or temporal disease analysis [95]. This could benefit image-guided surgery, in which training data is very scarce and difficult to obtain [96]. One way is to leverage synthetic data with ground truth information, adapting it to the real data. This approach has been successfully applied in natural images [97]. Reverse domain adaptation (*i.e.*, translating real data to synthetic data) is also a promising solution. Mahmood *et al.*, [39] generated synthetic endoscopy data with known depth information by using an anatomical colon model and a virtual endoscope. This simulated data was used for 3D reconstruction of real endoscopic images. Pan *et al.*, [30] translated MR data to generate synthetic PET images to infer missing patient scans for temporal analysis of Alzheimer’s disease [30]. Another area that could benefit from synthetic data is skin lesion detection [98].

**Table 1** Summary of DA studies in medical imaging categorized by DA methodology, task, modality, anatomy, and learning scenarios (S: Segmentation; C: Classification; 3DR: 3D Reconstruction).

DA Method	Framework	Task	Source & Target Domains	Anatomy	Learning Scenario	Publications
<b>Radiology</b>						
<b>Single Modality</b>						
DT	Reconstruction	S	X-ray (different demographics)	Lung	Unsupervised	Chen. et. al., [28]
		C	X-ray (different demographics)	Lung		Tang et. al., [100]
		S	Synthetic data → MRI	Brain		Gholami et. a. [99]
	Unidirectional	C	X-ray (different demographics)	Lung	Semi-supervised	Madani et. al., [46]
		C	Ultrasound (different sources)	Fetal Head		Yang et. al., [25]
LFST	Adversarial	S	X-ray (different disease states)	Lung	Unsupervised	Dong et. al., [104]
		S	Ultrasound (different sources)	Heart		Degel et. al., [26]
		S	MRI (different FLAIR sequences)	Brain		Orbes-Arteaga et. al., [78]
		S	MRI (moderate to severe TBI)	Brain		Kamnitsas et. al., [77]
		S	MRI (different disease types, demographics)	Brain		Novosad et. al., [106]
		S	MRI (different vendors)	Brain		Yan et. al., [109]
		S	MRI (cross-institutional)	Brain, Spine		Shanis et. al., [79]
	Divergence	S	X-ray (different disease types, demographics, contrast)	Lung		Venkataramani et. al., [72]
	Reconstruction	S	X-ray (different datasets)	Breast	Semi-supervised, Unsupervised	Oliveira et. al., [80]
	<b>Cross-Modality</b>					
DT	Reconstruction	S	CT → MRI	Lung	Unsupervised	Jiang et. al., [54]
		S	CT → X-Ray	Lung		Zhang et. al., [51]
		S	MRI ↔ CT	Heart		Chen et. al., [59]
		S	MRI → CT	Heart		Chartsias et. al., [11]
		S	CT ↔ MRI	Heart	Supervised	Zhang et. al., [41]
		S (3D)	CT ↔ MRI	Heart, Breast, Pancreas	Unsupervised	Cai et. al., [52]
		S	MRI → CT	Abdomen		Huo et. al., [12]
		S	MRI → CT, MRI (T1 → T2)	Abdomen, Brain		Liu et. al., [56]
		S	CT → MRI	Hip, Thigh, Pelvis		Hiasa et. al., [53]
	C	MRI → PET	Brain	Supervised	Pan et. al., [30]	
Unidirectional	S	MRI → CT	Brain	Unsupervised	Zhao et. al., [47]	
	3DR	CT → 3D rendered depth-map	Colon		Mahmood et. al., [39]	
LFST	Divergence	C	MRI → PET	Brain	Unsupervised	Zhu et. al., [71]
	Adversarial	S	CT → MRI	Abdomen		Yang et. al., [102]
		S	MRI → CT	Heart		Dou et. al., [103]
	Reconstruction	S (3D)	MRI → CT	Heart		Ouyang et. al., [81]
<b>Pathology</b>						
<b>Single Modality</b>						
DT	Unidirectional	C	WSI (different H&E stains)	Breast, Colon, Ovary	Unsupervised	Bentaieb et. al., [29]
LFST	Adversarial	C	WSI (different stains)	Breast		Lafarge et. al., [76]
		C	WSI (cross-institutional)	Prostate		Ren et. al., [107]
	S	WSI (different stains)	Colon	Supervised		Hou et. al., [110]
Divergence	S	Microscopy (different specimens)	Brain	Unsupervised	Chacon et. al., [74]	
<b>Cross-Modality</b>						
DT	Reconstruction	S	WSI (CK → PD-L1)	Lung	Unsupervised	Kapil et. al., [101]
	Unidirectional	S	WSI (H&E ↔ IF)	Breast, Bladder, Lung		Brieu et. al., [16]
LFST	Adversarial	C	WSI → Microscopy	Colon		Zhang et. al., [5]
<b>Ophthalmology</b>						
<b>Single Modality</b>						
DT	Unidirectional	S	Retinal fundus (multiple datasets)	Retina	Unsupervised	Zhao et. al., [111]
LFST	Adversarial	S	Retinal fundus (multiple datasets)	Retina		Javanmardi et. al., [105]
		S	Retinal fundus (multiple datasets)	Retina		Wang et. al., [108]
	Divergence	S	Retinal fundus (multiple datasets)	Retina		Zhuang et. al., [73]



## 5 Conclusions and Future Directions

Deep learning has been widely applied to medical imaging data analysis. However the lack of well-annotated images and the heterogeneity of multi-center medical imaging datasets are two key challenges for DL performance. DA has emerged as an effective approach for minimizing domain-shift and leveraging labeled data from distinct but related domains. FST-DA and DT-DA are two popular approaches to minimize the distribution divergence in multiple medical imaging studies exploring same-modality or cross-modality scenarios. They have proven to achieve good performance, particularly in unsupervised DA settings and organ segmentation tasks. Current approaches are primarily adversarial with domains being selected based on certain heuristics and underlying tasks. Extensive benchmarking studies are needed to quantify the domain relationship for different imaging modalities and to compare adversarial and non-adversarial approaches. Varying sample transferability and multi-modal domains for medical imaging are two other major issues. One strategy is to explore down-weighting or attention-based networks. Also alternative multi-modal frameworks such as MUNIT [30] can be explored. Finally, for certain application areas in medical imaging such as 3D reconstruction and temporal disease analysis where DA is relatively unexplored, synthetic data can be used.

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