A Review of Uncertainty Estimation and its Application in Medical Imaging

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Abstract—The use of AI systems in healthcare for the early screening of diseases is of great clinical importance. Deep learning has shown great promise in medical imaging, but the reliability and trustworthiness of AI systems limit their deployment in real clinical scenes, where patient safety is at stake. Uncertainty estimation plays a pivotal role in producing a confidence evaluation along with the prediction of the deep model. This is particularly important in medical imaging, where the uncertainty in the model's predictions can be used to identify areas of concern or to provide additional information to the clinician. In this paper, we review the various types of uncertainty in deep learning, including aleatoric uncertainty and epistemic uncertainty. We further discuss how they can be estimated in medical imaging. More importantly, we review recent advances in deep learning models that incorporate uncertainty estimation in medical imaging. Finally, we discuss the challenges and future directions in uncertainty estimation in deep learning for medical imaging. We hope this review will ignite further interest in the community and provide researchers with an up-to-date reference regarding applications of uncertainty estimation models in medical imaging.

I. INTRODUCTION

Deep learning systems achieve significant progress in medical image analysis, and are used widely for a wide range of tasks [1]–[6], such as tumor segmentation, disease diagnostics, and treatment planning. However, these systems can also introduce new risks and challenges, such as bias, errors, and lack of transparency. Imagine a deep learning system that is used to identify eye disease as either Diabetic Retinopathy (DR) or normal. The system has been trained on a large dataset of well-cleaned images of eye diseases collected from hospitals and is able to make predictions with high accuracy on the test image within the same distribution, as shown in Fig. I (A). However, there is still some uncertainty in its predictions, as some of the images in the open medical environments with low quality or Out-of-Distribution (OOD) are difficult

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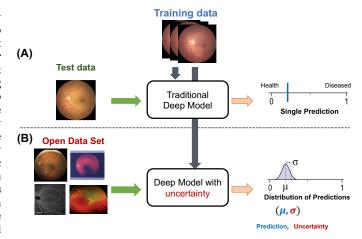


Fig. 1. The example of eye disease screening AI system in the open clinical environment. (A) Traditional deep models are often trained with closed-world assumption, *i.e*, the distribution of test data is assumed to be similar to the training data distribution. (B) However, when deployed in real clinical scenes, this assumption doesn't hold true leading to a significant drop in performance and producing an unreliable result. The uncertainty estimation provides a confidence score, which allows users to quantify the reliability of the model's output and to identify when the model may not be performing well.

to classify or contain a high degree of variability. For these low-quality/OOD cases, the transitional AI system may still provide a probability score indicating the likelihood that the eye is diseased. However, this prediction is not reliable.

Recently, trustworthy AI is proposed to address these challenges by incorporating principles such as explainability, robustness, and accountability into the design and development of AI systems, which intends to provide clinicians and patients with the confidence that the predictions and recommendations made by the AI are accurate and reliable [7], [8]. Uncertainty **Estimation** (or Uncertainty Quantification) of deep networks, as one key of trustworthy AI, refers to the process of predicting the uncertainty or confidence of a neural network's predictions [9]-[11]. Since it allows us to quantify the reliability of the network's output and to identify when the network may not be performing well. For example, when a clinician uses the system to analyze an open set image of the eye disease, the deep learning system still makes predictions with a high degree of accuracy, but it also produces an uncertainty estimation in its predictions, as shown in Fig. I (B). In this case, the clinician then would be afforded opportunities to take into account the uncertainty in the prediction and consider other factors such as the patient's medical history and any additional diagnostic tests, and either ignore predictions with high uncertainty or triage them for detailed, human review.

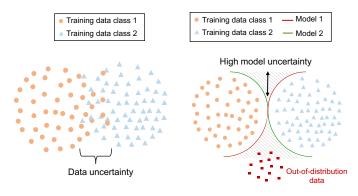


Fig. 2. Visualization of the aleatoric (data) and the epistemic (model) uncertainty for the classification model.

Therefore, it's important for the clinician to understand this uncertainty and how it may impact the decision making process.

Uncertainty estimation used in healthcare can be divided into interventional and non-interventional methods according to the doctor's involvement on the data:

- Interventional applications: Interventional safety-critical
 applications involve scenarios where errors can have
 severe consequences, such as cancer diagnosis. In such
 case, it is crucial to measure the model's confidence in
 its predictions. If the model exhibits high uncertainty in
 its predictions, the results need to be referred to experts
 for further diagnosis and intervention. This ensures that
 critical decisions are not solely based on uncertain predictions and that human expertise is involved in the decisionmaking process.
- Non-interventional applications: Non-interventional methods do not require expert intervention. They are used for preliminary screening of data, such as out-of-distribution (OOD) sample detection and anomaly detection. **OOD sample detection** refers to the identification of inputs that significantly differ from the training data, leading to potentially unreliable predictions. By estimating uncertainty, the model can flag such inputs as potentially problematic, triggering further analysis or human intervention. Abnormal detection is another non-interventional application, where the model makes incorrect predictions for abnormal cases that were not present in the training data. Uncertainty estimation helps in identifying instances where the model is likely to be incorrect, highlighting areas for model improvement or the need for additional training data.

By employing uncertainty estimation techniques in healthcare, both non-interventional and interventional applications can benefit from improved reliability and safety. The use of uncertainty estimation enhances the decision-making process, reduces risks, and ensures appropriate involvement of medical professionals in critical cases.

II. BACKGROUND OF UNCERTAINTY

A. Types of Uncertainty

Uncertainty in the context of deep learning models refers to the model's lack of confidence in its predictions. This can be thought of as a measure of the model's ignorance or ambiguity about the correct output for a given input. There are two main types of uncertainty to quantify in deep learning models [12], as shown in Fig. 2:

Aleatoric uncertainty (Data uncertainty): This type of uncertainty arises from inherent noise in the data, such as measurement error or ambiguous annotation, which cannot be reduced by collecting more data [9], [12]. Aleatoric uncertainty can be estimated by training the model to output a distribution over possible predictions, rather than a single point estimate. The aleatoric uncertainty will never get smaller, even if we master the problem.

Epistemic uncertainty (Model uncertainty): This type of uncertainty arises from a lack of knowledge or information about the underlying model or data distribution or insufficient model structure [12]. Epistemic uncertainty can be estimated by using methods such as Bayesian neural networks or ensembles of models. This kind of uncertainty can be (theoretically) reduced by using more complex models, collecting more data, or by using regularization techniques. In some uncertainty works, they also mention a special kind of uncertainty, **Distributional uncertainty**, which refers to the uncertainty in the model's predictions when the inputs belong to a different distribution than the training data, i.e., OOD. In deep learning, this can occur when the model encounters inputs that are significantly different from what it was trained on. The distributional uncertainty could belong to epistemic uncertainty.

B. Methods of Uncertainty Estimation

There are a few different approaches to estimating uncertainty in deep networks, as shown in Fig. 3, including:

- **Deterministic method:** Deterministic methods provide a deterministic estimate of uncertainty, meaning that they provide a single value or measure to represent the level of uncertainty associated with a prediction. These methods typically assume that the model is deterministic, and that the uncertainty can be estimated based on one single forward pass. The main advantage of them is their simplicity and computational efficiency. The common deterministic methods include evidential deep learning [13]–[17], and distance-based [18]–[20] methods.
- Bayesian Neural Networks (BNNs): BNNs are a type of deep learning model that explicitly model uncertainty by representing the model's parameters as random variables [21]–[24]. This allows BNNs to estimate uncertainty by quantifying the distribution of possible outputs for a given input, rather than just a single point estimate. An alternative to directly estimating model parameters is to approximate inference from multiple predictions of the model, which saves computational overhead [10]. In this method, Dropout [25] is often used as a regularization technique that involves randomly setting a percentage of

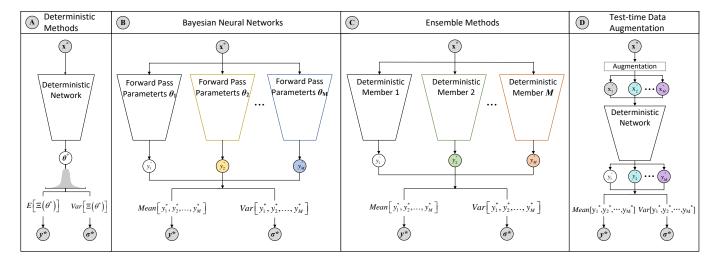


Fig. 3. The different methods of uncertainty estimation.

the inputs to a layer to zero during training. This can be seen as a way of approximating Bayesian inference by sampling different model architectures during training.

- Ensemble method: The ensemble method for uncertainty estimation in deep learning involves using multiple models to make predictions, and then aggregating the predictions to estimate uncertainty with the variance of the individual predictions serving as a measure of uncertainty [26]–[29]. This can be done by combining the outputs of multiple models, or by training an ensemble of models to make predictions.
- Test-time data augmentation: It is a method for uncertainty estimation that involves augmenting the test data with different perturbations, and then evaluating the model's performance on these perturbed inputs [30]–[32]. This allows the model to estimate its own uncertainty by evaluating how its predictions change for different inputs.

Each of these methods has its own advantages and disadvantages, and the best method will depend on the specific requirements of the task and the application.

III. APPLICATIONS IN MEDICAL IMAGING

A. Classification

The classification task is an important topic in the field of medical image processing. In recent years, with the explosive development of deep learning, numerous methods for medical image target classification have been explored. These methods have indeed achieved remarkable success in medical image classification tasks as well, even achieving results comparable to those of clinicians in some areas. However, most of these approaches have focused on improving the performance of the algorithms and ignored the reliability analysis of the model prediction results, which has become one of the important factors limiting the deployment of AI algorithm-based classification models in clinical practice. Therefore, developing AI models with uncertainty estimation for medical image classification tasks is essential to improve user confidence in deploying AI models as an aid to diagnosis in clinical

practice. Depending on the application domain, we will discuss uncertainty estimation for ophthalmology images [33]–[36], histopathology images [37]–[40], skin disease images [41]–[43], MRI images [44], [45], and chest radiographs [46]–[49].

Recently, several studies have been explored to introduce uncertainty theory to conduct trustworthy classification in ophthalmology images. In [33], Leibig et al. evaluated the dropout based Bayesian uncertainty measure for deep learning in diagnosing DR from fundus images and showed that it captures uncertainty better than direct alternatives. They computed meaningful uncertainty measures without adding additional labels for explicit uncertainty categories based on the connection between dropout networks and approximate Bayesian inference. Besides, they also demonstrated that uncertainty-informed decision referrals can improve diagnostic performance. For DR detection, Araújo et al. [34] proposed a novel deep learning-based DR grading system, which supports its decision by providing a medically interpretable explanation and an estimation of how confident that prediction is, indicating that the ophthalmologist to measure how much that decision should be trusted. Ayhan et al. [35] introduced an intuitive framework based on test-time data augmentation for quantifying the diagnostic uncertainty of deep neural networks for detecting DR. In addition, based on Bayesian neural networks, Jaskari et al. [36] further proposed an uncertaintyaware deep learning method for robust DR classification.

Moreover, inspired by the pathologist's actual practices and the automatic Whole Slide Image (WSI) classification system, Feng et al. [39] proposed a trusted multi-scale classification framework for the WSI based on uncertainty theory. In their study, a vision transformer was employed as the backbone for different branches to model the classification and evidential uncertainty theory was introduced to estimate the uncertainty of each magnification of a microscope. The final classification result is calculated by integrating the evidence from different magnifications. This method achieved excellent performance on two databases: Liver-Kidney-Stomach immunofluorescence WSIs [50] and Fibroma hematoxylin-eosin WSIs. Dolezal et al [38]. made high-confidence predictions for digital

histopathology with an uncertainty-based deep learning model. In this study, they introduced a clinically-oriented approach to uncertainty quantification for whole-slide images, evaluating uncertainty using dropout and calculating thresholds on training data to determine cutoffs for low and high confidence predictions. They trained models to identify lung adenocarcinoma and squamous cell carcinoma and demonstrated that high confidence predictions outperformed uncertain predictions in cross-validation and testing of two large external datasets spanning multiple institutions. Furthermore, Linmans et al [40] explored the introduction of predictive uncertainty estimation to detect OOD detection in digital pathology. This work provides a benchmark for evaluating popular methods on multiple datasets by comparing uncertainty estimates for within-distribution and OOD samples at the whole slide level.

In the field of skin lesion analysis, Molle et al. [41] first pointed out the limitations of approximating uncertainty inference based on Bayesian estimates and propose a novel uncertainty measure based on overlap of output distributions. And the effectiveness of the metrics was verified in the classification of skin lesion. In addition, Combalia et al. [42] explored the use of uncertainty estimation methods and metrics for deep neural networks and apply MC-Dropout for dermoscopic image classification. More comprehensive, Abdar et al. [43] introduced three uncertainty quantification methods, MC-Dropout, ensemble MC, and deep ensemble to address the uncertainty in skin cancer image classification, as well as proposed a novel hybrid dynamic Bayesian deep learning model that takes uncertainty into account based on the threebranch decision theory. This method achieved encouraging classification performance for skin cancer images.

In the field of Magnetic Resonance Image (MRI) analysis, Herzog et al. [44], proposed a Bayesian convolutional neural network to predict a probability for a stroke lesion on 2D MR images while generating corresponding uncertainty information about the reliability of the prediction. Prince et al. [45] employed the Variational Inference by elliptical slice sampling to quantify the uncertainty for classification of Adamantinomatous Craniopharyngioma from preoperative MRI. They developed a classification waiver mechanism using uncertainty estimation to support clinical noninvasive diagnosis of brain tumors in the future. In the field of chest radiographs analysis, to address the fact that traditional AI models may have poor generalization to unseen data due to overconfidence in prediction results, Ghesu et al. [46] proposed an automatic system for chest radiograph assessment based on the principles of information theory and subjective logic [51] based on the Dempster-Shafer framework [52] for modeling of evidence. Different from the uncertainty of the estimated region mentioned above, some researchers [46]-[49] use different methods of training convolutional neural networks with uncertainty labels to approach experts' judgments on chest radiographs. Irvin et al. [47] first constructed a large chest radiograph dataset with uncertainty labels to automatically detect the presence of 14 observations in radiology reports. To address this issue, Pham et al. [49] involved training cuttingedge convolutional neural networks that leverage hierarchical dependencies among abnormality labels. Additionally, they proposed incorporating the label smoothing technique to effectively handle uncertain samples, which constitute a substantial portion of nearly every Chest X-rays dataset. How to turn uncertain labels into definite labels to guide classification will be one of the hotspots of future research. After all, the cost of accurate labeling is too high and the time is longer.

In summary, although existing methods have made progress in evaluating prediction confidence for their respective tasks, there are still two limitations that require further improvement. Firstly, most previous studies on uncertainty in medical image classification utilize an MC-Dropout Bayesian-based approach, which are both stochastic and inefficient. Secondly, many of these studies are task-specific and lack end-to-end capability, making them less scalable. To overcome these limitations, it is worth exploring deterministic-based methods for medical image classification tasks, such as the evidential deep learning methods [13], [53]. They employ the deterministic network to calculate final prediction and corresponding uncertainty score with a single forward pass without sampling.

B. Segmentation

Semantic segmentation, a crucial task in computer vision and image processing, involves assigning semantic labels to every pixel of an input image from a range of predefined classes [68]. There is a growing urgency in the context of semantic segmentation to explore ambiguity estimation in medical image pixels. Indeed, uncertainty in semantic segmentation can generally be divided into two types: (1) ambiguity within the area or boundary surrounding the tissue, and (2) unknown semantic categorization of the region or boundary. In medical domain, uncertainty estimation for medical image segmentation can be roughly divided into Bayesian-based [69]-[75] and Non-Bayesian-based methods [76]–[90]. Bayesian-based methods enables the segmentation networks to learn a distribution over the network weights with uncertainty rather than a single pixel-wise estimate. To avoid computationally expensive by them, a variety of non-Bayesian methods have been developed, included Monte Carlo (MC) dropout based [76]-[82], ensemble-based [83]-[86] and Deterministic-based [87]–[92].

For the Bayesian-based methods, PU [69] first considered the task of learning a distribution over segmentation given an input in medical domain. Other methods [70]–[72] further improved the PU in terms of epistemic uncertainty and model efficiency. Sedai et al. [74] used Bayesian deep learning for retinal layer segmentation with uncertainty quantification. Then, Carannante et al. [75] used the first-order Taylor series approximation to propagate and learn the distribution of the model parameters for medical image segmentation.

To solve the problem of time overhead and accurate estimation of the posterior, the MC dropout-based methods were proposed. Nair et al. [77] first explored the multiple uncertainty estimates based on MC dropout in the context of deep networks for lesion detection and segmentation in medical image. Wickstrøm et al. [78] developed MC dropout in FCN and model interpretability in the context of semantic segmentation of polyps from colonoscopy images. Yu et

 $TABLE\ I$ The summary of uncertainty estimation methods for medical image classification.

Method	Year	Target	Estimation	Dataset	Use case
[33]	2017	Fundus image	MC-Dropout	Messidor [54]	DR detection
[35]	2020	Fundus images	Bayesian-based	Kaggle DR ^a & IDRiD [55]	DR detection
[34]	2020	Fundus images	Gaussian distribu-	Kaggle DR b , Messidor-2 [56], IDRID [55],	DR detection
			tion centered	DMR [57], and SCREEN-DR (private dataset)	
[36]	2022	Fundus images	Bayesian-based	EyePACS [58], KSSHP ^c , Messidor-2 [56], and APTOS ^d	DR detection
[37]	2021	Histology im-	Bayesian-based	GlaS Dataset [59] & Camelyon16 Patch-Based	Breast cancer
		ages		Benchmark [60]	
[38]	2022	Histology im-	Dropout	TCGA ^e & CPTAC ^f	Lung adenocarcinoma and
		ages	_		lung squamous cell carci-
					noma
[39]	2022	Histology im-	Evidential-based	LKS dataset [50] & Fibroma (private dataset)	Liver Kidney Stomach
		ages			
[40]	2023	Histology im-	Deep ensemble	Camelyo17 challenge [61] and the PANDA chal-	OOD detection in digital
		ages		lenge [62]	pathology
[41]	2019	Dermoscopic	MC-Dropout	HAM10000 dataset [63]	Skin lesion classification
		image			
[42]	2020	Dermoscopic	MC-Dropout	ISIC2018 dataset [64] and ISIC2019 dataset 8	Skin disease classification
		image			
[43]	2021	Dermoscopic	Deep ensemble	Kaggle Skin Cancer dataset h & ISIC2019	Skin disease classification
		image		dataset ⁱ	
[44]	2020	MRI	MC Dropout	private dataset	MRI based stroke analysis
[45]	2023	MRI	Variational infer-	private dataset	MRI based Adamantinoma-
			ence		tous Craniopharyngioma
[46], [65]	2019&2021	X-Ray	MC-Dropout	ChestX-Ray8 [66] & PLCO [67]	Chest Radiograph Assess-
					ment

^ahttps://www.kaggle.com/c/diabetic-retinopathy-detection

al. [79] introduced the MC dropout in a semi-supervised framework and presented an uncertainty-aware model for left atrium segmentation from 3D MR images. Wang et al. [81] developed test time augmentation method to analyze epistemic and aleatoric uncertainty for MC sampling-based medical image segmentation tasks at both pixel and structure levels.

Another simple way to produce uncertainty for medical image segmentation is to use an ensemble of deep networks [83]–[86], [93]. Mehrtash et al. [84] studied predictive uncertainty estimation by using multi-FCNs ensembling. Cao et al. [93] then developed an uncertainty aware model for semi-supervised ABUS mass segmentation based on ensemble learning. Guo et al. [86] developed a globally optimal label fusion algorithm based on ensemble learning for short-axis cardiac MRI segmentation.

Unfortunately, the above methods cannot estimate the uncertainty of medical image segmentation with a single forward pass. Therefore, deterministic uncertainty estimation is proposed to train deterministic deep models with a single forward pass at test time. Amersfoort et al. [20] exploited the ideas of radial basis function networks to devise deterministic uncertainty estimation. Mukhoti et al. [19] first extended deep deterministic uncertainty to semantic segmentation using feature space densities. Judge et al. [90] implemented a contrastive method to learn a joint latent space which encodes a

distribution of valid segmentations. Recently, evidential-based learning approaches [87]–[89] have been proposed for medical image segmentation due to their robustness and efficiency. As stated in [88], they treat neural network predictions as subjective opinions by parameterizing the class probabilities of the segmentation as a Dirichlet distribution. Huang et al. [89] computed a belief function at each voxel for each modality and then used Dempster's rule for multi-modality medical image segmentation.

In what follows, we briefly discuss the advantages and disadvantages of uncertainty estimation in medical image segmentation. Bayesian-based methods cleverly consider learning a distribution over segmentation given an input in medical domain, but their training process is complicated. The simple way to generate uncertainty for medical image segmentation is ensemble-based methods, but often require more training time and computational burden. MC dropout-based methods are the most common in medical image segmentation, but often requires multiple sampling to generate uncertainty through multiple forward passes. Recently, deterministic-based methods have attracted great attention, which only provide uncertainty for each pixel in medical images through the single forward pass. Although these methods sacrifice certain segmentation performance, their robustness and ability

^bhttps://www.kaggle.com/c/diabetic-retinopathy-detection

^chttps://www.duodecimlehti.fi/duo15766

dhttps://www.kaggle.com/c/aptos2019-blindness-detection/overview/aptos-2019

ehttps://portal.gdc.cancer.gov/projects/TCGA-LUSC

fhttps://www.cancerimagingarchive.net/collections/

ghttps://www.kaggle.com/andrewm/isic-2019

https://www.kaggle.com/fanconic/skin-cancer-malignant-vs-benign

ⁱhttps://www.kaggle.com/andrewm/isic-2019

 $\label{thm:table II} The summary of uncertainty estimation methods for medical image segmentation.$

Method	Year	Target	Estimation	Dataset	Use case
[94]	2017	3D MRI	MC-Dropout	ADNI dataset [95]	Volumetric segmentation
[96]	2018	skin image	MC-Dropout	ISIC 2017 dataset [97]	Skin lesion segmentation
[98]	2018	3D MRI	MC-Dropout	BraTS 2017 dataset [99]	Volumetric uncertainty
[100]	2018	3D MR	MC-Dropout	private dataset	Multi-task for segmentation
					and regression
[101]	2018	2D MRI	MCMC sampling	private dataset	Brain image segmentation
			+ Bayesian MRF		
[77]	2018	3D MRI	MC-Dropout	private dataset	Lesion segmentation, 4 un-
					certainty measures
[102]	2018	2D MRI	MC-Dropout	private dataset	Brain Tumor Cavity Seg-
					mentation
[103]	2018	3D MRI	MCMC sampling	ISLES 2015 dataset [104]	Ischemic stroke lesion seg-
					mentation
[74]	2018	OCT	MC-Dropout	private dataset	Retinal Layer Segmentation
[105]	2018	2D MRI	MC-Dropout	private dataset	Inter-observer Variability
[106]	2019	CT	MC-Dropout	NIH pancreas dataset [107]	Organ Segmentation
[108]	2019	OCT	MC-Dropout	private dataset	Anomaly Detection
[79]	2019	3D MRI	MC-Dropout	Atrial Segmentation Challenge [109]	Semi-supervised Segmenta-
					tion
[81]	2019	MRI	Test-time augmen-	private dataset	Aleatoric uncertainty esti-
			tation		mation
[70]	2019	2D CT, MRI	Probabilistic Unet	LIDC-IDRI lung CT [110] and in-house prostate	Multi-scale
				MR dataset	
[111]	2019	2D MRI	MCMC sampling	private dataset	Brain image segmentation
			+ Bayesian MRF		_
[76]	2020	2D CT	MCMC sampling	private dataset	renal tumor
[84]	2020	2D MRI & 2D	Ensemble	BraTS [99], ACDC [112], PROSTATEx [113] and	Brain tumor & Ventricular
5003	2020	cine MR		PROMISE12 [114]	& prostate
[93]	2020	2D ABUS &	Ensemble	private dataset	ABUS Mass Segmentation
50.50	2021	2D BUS		D TTG 20400 2040 1	
[87]	2021	3D MRI	Evidential deep	BraTS 2018&2019 dataset [99]	Belief function theory and
5007	2022	20.101	learning	D 777 2040 1	evidential fusion
[88]	2022	3D MRI	Evidential deep	BraTS 2019 dataset [99]	Subjective logic theory and
5007	2022	an Ha W	learning	CANTILL THE ON THE O	Dirichlet distribution
[90]	2022	2D US, X-ray	Joint latent space	CAMUS [115], HMC-QU [116], Shenzen [117]	Cardiac and lung segmenta-
				and JSRT [118] dataset	tion

to detect OOD data are enhanced. In the future, there are many open research directions on uncertainty quantification in medical image segmentation that should be considered. First, how to generate more robust and calibrated uncertainty during the segmentation. Second, how to make better use of uncertainty to guide the improvement of segmentation performance. In addition, how to introduce uncertainty into the training process is also beneficial to the performance of medical image segmentation. In short, the application of uncertainty generation in medical image segmentation will be one of the emerging directions for reliable and explainable medical artificial intelligence.

C. Other tasks

As an important analytical tool for trustworthy learning, uncertainty estimation is also equipped in other medical image assessment tasks, such as image registration [119]–[124], image reconstruction [30], [125]–[129], image denoising [130], super-resolution [131]–[133], counting [134], image detection [135] and tumor growth prediction [136].

Image registration is the foundation for many image-guided medical tasks. Estimating the uncertainty for image registration enables surgeons to assess the surgical risk based on the reliability of the registered image. If surgeons receive inaccurately calculated registration uncertainty and then misplace unwarranted confidence in the alignment results, severe

consequences may result. Luo, et al [119] divided the registration uncertainty into two aspects: transformation uncertainty and label uncertainty. Le Folgoc, et al [120] investigated uncertainty quantification under a sparse Bayesian model of medical image registration. They implemented an exact inference scheme based on reversible jump Markov Chain Monte Carlo sampling to characterize the transformation posterior distribution. Madsen, et al [121] and Luo et al. [122] also viewed surface registration as a probabilistic inference problem and use Gaussian Process Morphable Model as the prior model. Markiewicz et al. [123] applied the uncertainty analysis to the multi-modal registration between PET and MRI images. Xu et al. [124] introduced the mean-teacher based registration framework. Instead of searching for a fixed weight, the teacher enables automatically adjusting the weights of the spatial regularization and temporal consistency regularization by taking advantage of the appearance uncertainty and the transformation uncertainty.

Image reconstruction is also the foundation task for medical image analysis. The goal of medical image reconstruction is to restore a high-fidelity image from partially observed measurements. Measuring the uncertainty in the process of reconstruction is critical. Zhang et al. [125] presented MRI reconstruction method that dynamically selects the measurements to take and iteratively refines the prediction in order to best reduce the reconstruction error and, thus, its uncertainty.

Edupuganti et al. [126] leveraged variational autoencoders to develop a probabilistic reconstruction scheme and exploit MC sampling to generate the uncertainty from the posterior of the image. Narnhofer et al. [129] proposed a deterministic MRI Reconstruction which introduces a Bayesian framework for uncertainty quantification in single and multi-coil undersampled MRI reconstruction exploiting the total deep variation regularizer.

In addition, there are various efforts devoted to exploring uncertainty estimation for medical image analysis tasks. Tanno et al. [131]-[133] focused on super-resolution and propose to account for intrinsic uncertainty through a heteroscedastic noise model and for parameter uncertainty through approximate Bayesian inference, and integrate them to quantify predictive uncertainty over the output. Cui et al. [130] introduced the uncertainty estimation into PET denoising task. They proposed a Nouveau variational autoencoder based model using quantile regression loss for simultaneous PET image denoising and uncertainty estimation. Eaton et al. [134] leveraged the counting task by introducing Predictive Intervals estimation to calculate the counting intervals. Furthermore, Ozdemir et al. [135] introduced uncertainty estimation into pulmonary nodule detection and Petersen et al. [136] exploited it to the glioma growth. These attempts have demonstrated the importance of introducing uncertainty analysis into medical image analysis.

In general, as the fundamental tasks for medical image analysis, image registration and image reconstruction tasks have received the most attention when it comes to the application of uncertainty estimation. Estimating the uncertainty for these two tasks enables surgeons to assess the operative risk based on the trustworthiness of the registered or reconstructed image data. In addition, it is noted that uncertainty estimation has been less studied for other tasks such as image denoising, counting, and detection which are also important components of medical analysis. More future research work would be directed toward these tasks.

IV. DISCUSSION AND CONCLUSION

Uncertainty estimation is a crucial aspect of deep learning in medical imaging, and it is an active area of research. However, there are several challenges and limitations associated with uncertainty estimation:

- Lack of ground truth for uncertainty: One of the main challenges in uncertainty estimation is the lack of ground truth for uncertainty in many medical applications. This makes it difficult to accurately estimate the uncertainty of deep learning models and evaluate the performance of different uncertainty estimation methods.
- Computational complexity: The estimation of uncertainty in deep models can be computationally complex, especially for large and complex models. This can make it difficult to scale uncertainty estimation to use uncertainty estimation in real-time clinical systems.
- Trade-off between accuracy and reliability: In practice, a model can have high accuracy but low reliability, or vice versa. Accuracy and reliability are complementary

metrics that provide different perspectives on a model's performance, and both are important to consider when evaluating deep learning models. The goal should be to achieve high accuracy and reliability, but the trade-off between the two may vary depending on the specific use case and requirements of the model.

• Limited empirical evaluations: Finally, there is a limited empirical evaluation of uncertainty estimation methods, especially in real clinical scenarios. This makes it difficult to compare and evaluate different methods, and to determine which methods are most effective and efficient in different tasks. However, one potential solution to address this issue is the utilization of different expert annotations, as demonstrated in [47]. It was annotated by different experts to capture the inherent uncertainty in the interpretation of radiographs. By leveraging such diverse expert annotations, it becomes possible to better understand and quantify uncertainty in clinical scenarios, facilitating more accurate evaluations of uncertainty estimation methods.

Overall, these challenges and limitations need to be addressed in order to fully realize the potential of uncertainty estimation in deep learning. By incorporating uncertainty estimation into AI systems, we can make them more robust and trustworthy in their predictions and decision-making processes, which can ultimately lead to improved patient outcomes.

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Method	Year	Target	Estimation	Dataset	Task
[119]	2019	3D MRI	Entropy	CUMC12 [137] and BraTS [99] datasets	Image registration
[131],	2017,	3D MRI	Variational	WU-Minn HCP [138], Lifespan [139],	Super-resolution
[132]	2017,	JD WIKI		Prisma [140], and Pathology [141] datasets	Super-resolution
	2019	3D CT	Dropout MC-Dropout	LUNA16 [142] dataset	Pulmonary Nodule Detec-
[135]	2017	SD C1	WIC-Diopout	LUNATO [142] dataset	tion
F12.47	2010	0D 11 (4)	D ' 1 1	C 11 12 4 1 51 421 1 WA CH 51 441 1 4 4	*****
[134]	2019	2D histopatho-	Bayesian-based:	Cell histology [143] and WMH [144] datasets	Counting task
540.63	2010	logical image	PI estimate		
[136]	2019	MRI	Probabilistic Unet	private dataset	Glioma Growth Prediction
[120]	2017	2D medical im-	MCMC	Private dataset	Image registration
		age			
[125]	2019	2D MRI	Bayesian-based	fastmri [145] and ImageNet [146] datasets	Image reconstruction
[121]	2020	CT	Gaussian process	Public face [147] and private femur bones	Surface Registration
				datasets	
[122]	2020	MRI	Gaussian process	RESECT [148] and private MIBS datasets	Image Registration
[127]	2021	PET and MRI	MC dropout	Private dataset	Image reconstruction
[133]	2021	3D MRI	Variational	WU-Minn HCP [138], Lifespan [139],	Super-resolution
			Dropout	Prisma [140], and Pathology [141] datasets	_
[123]	2021	PET and MRI	MC sampling	Private dataset	Image registration
[126]	2021	MRI	MC sampling	Mridata [149]	Image reconstruction
[128]	2021	3D MRI	Gaussian process	OASIS-3 brain [150] dataset	Biological age detection
[130]	2022	PET	Quantile Regres-	¹¹ C-DASB [151]	PET Denoising
[100]			sion	[]	
[124]	2022	CT and MRI	MC dropout	Private dataset	Image registration
[129]	2022	MRI	Deterministic	fastMRI [152] dataset	Image reconstruction

BraTS [99] and private dataset

 $\label{thm:thm:thm:equiv} TABLE~III$ The summary of uncertainty estimation methods for the other medical image tasks.

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MRI and FET-

PET

MCMC

[30]

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