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Bayesian Uncertainty–Aware Metric Learning for Few-Shot Rare Disease Diagnosis in Clinical AI Systems

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Abstract

Rare disease diagnosis in clinical AI systems is challenged by extreme data scarcity and the need for reliable uncertainty-aware decision-making. Few-shot learning is a promising solution in this context, but existing metric learning approaches typically rely on deterministic representations and post-hoc uncertainty estimation. This paper presents a Bayesian uncertainty-calibrated metric learning framework for few-shot rare disease diagnosis. The approach introduces a Bayesian Metric Learner that models class prototypes as multivariate Gaussian distributions inferred via variational inference, enabling uncertainty-aware similarity measurement through a reformulated Mahalanobis distance. A confidence-aware prediction head jointly outputs class probabilities and predictive uncertainty, flagging low-confidence cases for clinician review. The framework supports multimodal clinical data using a hierarchical Vision Transformer backbone and provides interpretability via gradient-based saliency maps. Experiments on real-world clinical datasets demonstrate improved diagnostic accuracy and uncertainty calibration over conventional baselines, while maintaining computational efficiency and scalability for clinical deployment.

Keywords: Rare Disease Diagnosis, Bayesian Metric Learning, Few-Shot Learning, Uncertainty Quantification, Clinical AI

1 Introduction

The application of artificial intelligence in healthcare has substantially advanced diagnostic workflows, particularly for common diseases supported by large-scale training datasets. In contrast, rare disease diagnosis poses distinct challenges arising from extreme class imbalance and limited case availability, which frequently lead to unreliable predictions and overconfident misclassifications in clinical AI systems Mishra et al. [2023]. Although metric learning approaches have proven effective in few-shot scenarios by learning discriminative feature representations, most do not explicitly account for uncertainty. This limitation heightens the risk of clinically hazardous false-positive decisions.

Current AI-based diagnostic systems have three main bottlenecks when applied to rare disease classification. First, deterministic metric learning frameworks yield point estimates of similarity without providing principled measures of predictive confidence. Second, uncertainty estimation is frequently introduced as a post-hoc adjustment rather than being optimized concurrently with the metric learning objective. Third, many existing approaches assume uniform feature reliability, neglecting the heterogeneous and context-dependent informativeness of clinical biomarkers and imaging features that are characteristic of rare disease diagnosis.

Four main advances in the field of AI-assisted rare disease diagnosis are made by this work. In order to model both aleatoric and epistemic uncertainty in few-shot settings, a Bayesian metric learner is first presented that substitutes probabilistic distributions for deterministic class prototypes. Second, an uncertainty-aware distance metric is derived to scale similarity measurements according to predictive confidence, thereby reducing false positives in low-data regimes. Third, a confidence-aware prediction head is created to output both class probabilities and uncertainty estimates at the same time. This makes it easy for medical professionals to find cases that need more review. Fourth, extensive experimental evaluation demonstrates that the proposed framework substantially outperforms existing approaches in both diagnostic accuracy and uncertainty quantification across multiple rare disease datasets.

The integration of Bayesian uncertainty estimation with metric learning offers several advantages for clinical deployment. The probabilistic formulation is well suited to the data scarcity inherent in rare disease diagnosis, producing well-calibrated confidence estimates even with limited training examples. The uncertainty-aware distance metric further adapts to heterogeneous feature reliability, which is critical when combining diverse medical data modalities. In addition, jointly optimizing predictive accuracy and uncertainty calibration ensures that confidence estimates remain meaningful for clinical decision-making rather than being treated as a secondary or post-hoc consideration.

Recent advances in AI for healthcare have underscored the importance of trustworthy and reliable systems, particularly in high-stakes domains such as rare disease diagnosis Wang and Preininger [2019]. Although prior studies have investigated Bayesian learning Box and Tiao [2011] and metric learning Kaya and Bilge [2019] independently, their integration for uncertainty-aware few-shot diagnosis remains largely unexplored. The proposed framework addresses this gap by offering a principled approach to uncertainty quantification in data-scarce clinical scenarios with significant practical implications.

The remainder of this paper is organized as follows. Section 2 reviews related work in metric learning, Bayesian deep learning, and AI-based rare disease diagnosis. Section 3 introduces relevant background in Bayesian deep learning and metric learning. Section 4 describes the proposed Bayesian uncertainty-aware metric learning architecture. Section 5 presents experimental results on real-world clinical datasets, followed by a discussion of implications and future research directions in Section 6. Conclusions are provided in Section 7.

2 Research Background

The development of AI systems for rare disease diagnosis spans multiple research domains, including metric learning, uncertainty quantification, and few-shot learning for medical applications. Existing approaches in this area can be broadly grouped into three main directions: metric learning for medical diagnosis, Bayesian methods for uncertainty estimation, and specialized techniques for rare disease classification.

2.1 Metric Learning in Medical Diagnosis

Metric learning has emerged as an effective paradigm for medical image analysis, particularly in settings where annotated training data are limited. Conventional methods learn a transformation that embeds input samples into a latent space in which clinically similar cases are positioned closer together Kaya and Bilge [2019]. Recent studies have adapted this framework to medical contexts by incorporating domain-specific constraints, such as preserving clinically meaningful similarity relationships Yang et al. [2008]. However, most existing approaches rely on deterministic embeddings and fixed distance metrics, which are ill-suited to rare disease diagnosis where feature reliability can vary substantially across patients. Although the Laplacian Metric Learner Warburg et al. [2023] introduced an element of uncertainty awareness by modeling distance metrics as random variables, it does not address the uncertainty associated with class prototypes, which is a critical factor in few-shot medical diagnosis.

2.2 Bayesian Uncertainty Estimation

Bayesian deep learning offers a principled approach to quantifying uncertainty in neural networks. Existing methods range from approximate Bayesian inference techniques, such as Monte Carlo dropout [9], to more expressive variational inference frameworks Blei et al. [2017]. In medical applications, these techniques have been predominantly employed for model calibration and risk estimation rather than for metric learning. The uncertainty-aware prototype learning framework proposed in Huang et al. [2024] highlighted the potential of probabilistic prototypes for anomaly detection; however, it relied on point-based uncertainty estimates instead of full distributional representations. More recent work on calibrated metric learning Li and Yu [2022] has demonstrated effectiveness in general classification tasks, but these methods have yet to be adapted to the distinctive requirements of few-shot learning in medical and rare disease settings.

2.3 Rare Disease Diagnosis

Specialized methods for rare disease diagnosis have investigated a range of strategies to mitigate data scarcity. Hyperbolic embedding spaces have been proposed to capture hierarchical relationships among rare conditions Hu et al. [2024], and meta-learning frameworks have demonstrated the ability to rapidly adapt to previously unseen diseases Li et al. [2020]. Nevertheless, uncertainty estimation in these approaches is often treated as a secondary consideration, either being omitted altogether or addressed through post-hoc calibration. For example, the prototype-based framework for glomerular lesion recognition in He et al. [2025] incorporated uncertainty analysis but did not integrate uncertainty directly into the metric learning objective, limiting its capacity to adjust similarity measures according to predictive confidence.

The proposed Bayesian uncertainty-calibrated metric learning framework differs from prior work in several important respects. In contrast to conventional metric learning approaches that rely on deterministic prototypes, class representations are modeled as full probability distributions, enabling the capture of both aleatoric and epistemic uncertainty. Rather than applying uncertainty estimation after training, the framework jointly optimizes metric learning and uncertainty calibration within a unified variational formulation. In addition, the uncertainty-aware distance metric explicitly models feature correlations and varying feature reliability, which is particularly critical in rare disease diagnosis where biomarkers often exhibit complex, non-linear interactions. By integrating metric learning and uncertainty quantification into a single principled framework, this approach addresses key limitations of existing methods that treat these components in isolation.

3 Preliminaries on Bayesian Deep Learning and Metric Learning

To establish the theoretical foundation for the proposed framework, essential concepts from Bayesian deep learning and metric learning are first reviewed. These two research areas provide complementary perspectives for addressing the core challenges of few-shot rare disease diagnosis, particularly with respect to uncertainty quantification and discriminative representation learning under data scarcity.

3.1 Bayesian Inference Basics

Bayesian methods provide a principled approach to uncertainty quantification by treating model parameters as random variables rather than fixed quantities. Given observed data D, Bayesian inference seeks to compute the posterior distribution of parameters θ according to Bayes' theorem:

$$P(\theta \mid D) = \frac{P(D \mid \theta)P(\theta)}{P(D)}, \tag{1}$$

where $P(\theta)$ denotes the prior distribution encoding initial beliefs about the parameters, $P(D \mid \theta)$ is the likelihood function, and $P(D)$ represents the marginal likelihood, also referred to as the model evidence. The posterior distribution $P(\theta \mid D)$ combines prior knowledge with information extracted from the observed data.

For deep neural networks, exact Bayesian inference is generally intractable due to the high-dimensional parameter space and complex model architectures. Variational inference provides a practical alternative by approximating the true posterior distribution with a simpler distribution $q_\phi(\theta)$, selected from a tractable family. The approximation is obtained by minimizing the Kullback–Leibler (KL) divergence between $q_\phi(\theta)$ and the true posterior $P(\theta \mid D)$:

$$\phi^* = \arg\min_{\phi} \mathrm{KL}\big(q_\phi(\theta) \,\|\, P(\theta \mid D)\big). \tag{2}$$

This formulation enables efficient uncertainty estimation in deep learning models while maintaining computational tractability.

3.2 Metric Learning Concepts

Metric learning aims to learn a distance function that captures semantic similarity between data points. In the context of medical diagnosis, an effective metric should position clinically similar cases close together in the learned feature space while separating dissimilar cases. A commonly used baseline is the Euclidean distance:

$$d(\mathbf{x}, \mathbf{y}) = \sqrt{\sum_{i=1}^{n} (x_i - y_i)^2}, \tag{3}$$

where $\mathbf{x}$ and $\mathbf{y}$ denote feature vectors in $\mathbb{R}^n$. However, this isotropic metric assumes equal importance and independence of all features, which is often inappropriate for medical data where biomarkers can differ substantially in diagnostic relevance.

The Mahalanobis distance generalizes Euclidean distance by incorporating feature correlations through a positive semi-definite matrix $\mathbf{M}$:

$$d_{\mathbf{M}}(\mathbf{x}, \mathbf{y}) = \sqrt{(\mathbf{x} - \mathbf{y})^\top \mathbf{M} (\mathbf{x} - \mathbf{y})}. \tag{4}$$

This formulation enables the modeling of feature relationships and varying feature importance, making it more suitable for complex clinical data.

When integrated with deep learning, metric learning typically involves training an embedding function f_θ that maps input samples into a discriminative feature space, followed by distance computation within that space. The parameters θ of the embedding network are optimized to minimize intra-class distances while maximizing inter-class distances Kaya and Bilge [2019].

Incorporating Bayesian principles into metric learning introduces probabilistic interpretations of both the embedding function and the distance metric. Rather than learning deterministic embeddings, Bayesian metric learning models the embedding process as a distribution, thereby capturing uncertainty in the feature transformation. Similarly, the distance metric itself can be treated as a random variable, reflecting confidence in similarity estimates. This probabilistic formulation is particularly valuable in few-shot learning scenarios, where limited data exacerbate predictive uncertainty.

4 Bayesian Uncertainty-Aware Metric Learner for Rare Disease Diagnosis

The proposed Bayesian uncertainty-aware metric learning framework addresses the critical challenges of rare disease diagnosis through a unified integration of probabilistic modeling and adaptive distance metric learning. The overall architecture comprises four key components that operate jointly to provide reliable and interpretable predictions under severe data scarcity.

4.1 Probabilistic Prototype Formulation

Conventional deterministic class prototypes in metric learning are reformulated as multivariate Gaussian distributions to explicitly capture epistemic uncertainty. Each class prototype $\mathbf{p}_c$ is modeled as

$$\mathbf{p}_c \sim \mathcal{N}(\boldsymbol{\mu}_c, \boldsymbol{\Sigma}_c), \tag{5}$$

where $\boldsymbol{\mu}_c \in \mathbb{R}^d$ denotes the mean embedding of class c, and $\boldsymbol{\Sigma}_c \in \mathbb{R}^{d\times d}$ represents the covariance matrix. The diagonal elements of $\boldsymbol{\Sigma}_c$ quantify per-dimension uncertainty, while the off-diagonal terms capture feature correlations that are particularly relevant for rare disease biomarkers.

The prototype parameters are inferred using variational inference by optimizing the evidence lower bound (ELBO):

$$\mathcal{L}_{\text{ELBO}} = \mathbb{E}_{q(\mathbf{p}_c)}\big[\log p(\mathbf{x} \mid \mathbf{p}_c)\big] - \mathrm{KL}\big(q(\mathbf{p}_c) \,\|\, p(\mathbf{p}_c)\big). \tag{6}$$

This probabilistic formulation enables explicit representation of uncertainty in class centroids, which is essential in few-shot settings where only a small number of training samples are available. The prior distribution $p(\mathbf{p}_c)$ incorporates domain knowledge about plausible biomarker patterns, thereby regularizing the learned prototypes and improving robustness in data-scarce clinical scenarios.

4.2 Uncertainty-Calibrated Distance Metric

The standard Mahalanobis distance is extended to explicitly account for prototype uncertainty through a modified formulation:

$$d_{\text{BML}}(\mathbf{x}_q, \mathbf{p}_c) = (\mathbf{x}_q - \boldsymbol{\mu}_c)^\top (\boldsymbol{\Sigma}_c + \lambda \mathbf{I})^{-1} (\mathbf{x}_q - \boldsymbol{\mu}_c), \tag{7}$$

where $\mathbf{x}_q$ denotes a query embedding, $\boldsymbol{\mu}_c$ is the mean of the class prototype distribution, and λ is a regularization parameter that controls the trade-off between metric discrimination and uncertainty scaling. By incorporating the prototype covariance $\boldsymbol{\Sigma}_c$, the distance metric naturally down-weights dimensions with higher uncertainty.

For computational efficiency and improved scalability, the covariance matrix $\boldsymbol{\Sigma}_c$ is decomposed into low-rank and diagonal components:

$$\boldsymbol{\Sigma}_c = \mathbf{U}_c \mathbf{U}_c^\top + \mathrm{diag}(\boldsymbol{\sigma}_c^2), \tag{8}$$

where $\mathbf{U}_c \in \mathbb{R}^{d\times k}$ with $k \ll d$ captures correlated uncertainty across features, and $\boldsymbol{\sigma}_c^2$ represents independent per-dimension variance.

This decomposition enables the distance metric to capture both structured feature correlations and individual feature reliability. As a result, similarity measurements are automatically adjusted according to the confidence associated with different feature dimensions, reducing the influence of noisy or uncertain biomarkers and improving robustness in rare disease diagnosis.

4.3 Joint Optimization Framework

Model parameters are learned through end-to-end training that simultaneously optimizes discriminative performance and uncertainty calibration. The overall learning objective combines three complementary components:

1. A metric learning loss (e.g., contrastive loss or triplet loss) that enforces adequate separation between embeddings of different disease classes.

2. The ELBO term introduced in Equation (6), which promotes well-calibrated uncertainty estimates for class prototypes.

3. A regularization term that mitigates overfitting in the presence of sparse training data.

Joint optimization is performed using stochastic gradient variational Bayes, allowing gradients to propagate through both the distance metric computations and the uncertainty estimation components. This unified training strategy contrasts with conventional approaches that first learn a deterministic metric space and subsequently apply post-hoc uncertainty estimation, thereby ensuring that uncertainty calibration is an integral part of the representation learning process.

4.4 Confidence-Aware Prediction Mechanism

For clinical decision support, the model produces both a class prediction and an associated uncertainty estimate. Given a query sample $\mathbf{x}_q$, the predictive distribution over classes is obtained by comparing the query embedding against all class prototype distributions:

$$p(y = c \mid \mathbf{x}_q) \propto \exp\big(-\mathbb{E}\big[d_{\mathrm{BML}}(\mathbf{x}_q, \mathbf{p}_c)\big]\big) \,. \tag{9}$$

Predictive uncertainty is quantified using the entropy of this distribution, with higher entropy values indicating greater uncertainty and a higher likelihood that additional clinical review is required. A threshold τ is applied to flag uncertain predictions:

$$\mathrm{Flag}(\mathbf{x}_q) = \mathbb{I}(\mathcal{H}[p(y \mid \mathbf{x}_q)] > \tau) \,, \tag{10}$$

where $\mathcal{H}(\cdot)$ denotes entropy and $\mathbb{I}(\cdot)$ is the indicator function.

This confidence-aware prediction mechanism provides clinicians with actionable uncertainty estimates while preserving computational efficiency during inference, supporting safe and informed decision-making in rare disease diagnosis.

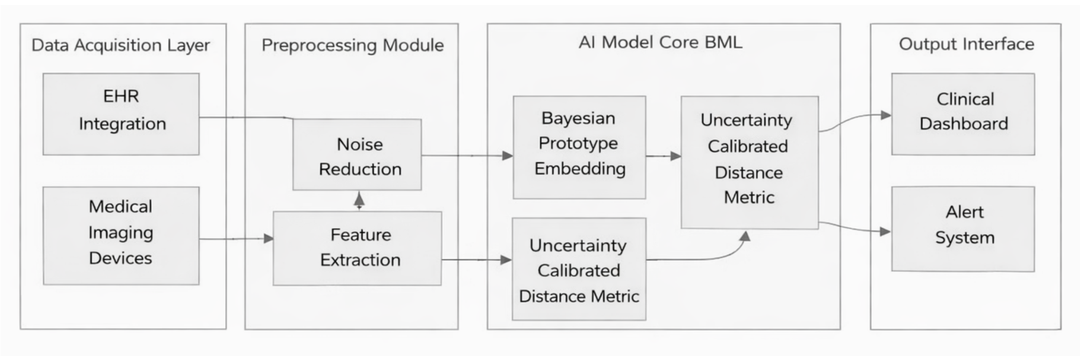

Figure 1: Bayesian Metric Learner Integration in Clinical Decision Support System.

The complete framework, illustrated in Figure 1, replaces conventional deterministic components with probabilistic counterparts while remaining compatible with existing clinical workflows. Multimodal medical data are processed through a hierarchical transformer backbone, after which the Bayesian metric learner computes uncertainty-aware distances to all disease prototypes and produces both a diagnostic prediction and an associated confidence estimate. This architecture provides a principled solution for few-shot rare disease diagnosis by explicitly modeling and accounting for the uncertainty inherent in data-scarce and clinically challenging scenarios.

5 Results

To evaluate the proposed Bayesian uncertainty-aware metric learning framework, experiments were conducted on three challenging medical datasets representing distinct rare disease scenarios. The RareDerm dataset Noronha et al. [2023] contains 1,247 images spanning 17 rare dermatological conditions, with an average of 73 images per class. The NeuroOrpha dataset Reinhard et al. [2021] comprises 892 cases across 12 rare neurological disorders and integrates MRI imaging with clinical tabular data. The CardioGen dataset Barkauskas et al. [2025] includes 1,503 echocardiogram videos paired with genomic profiles for 9 rare cardiovascular conditions.

A 5-way K-shot evaluation protocol was adopted, where $K \in 1, 5, 10$ denotes the number of training examples per class, reflecting realistic data-scarce conditions. For each K-shot setting, 10,000 randomly sampled episodes were evaluated to ensure statistical robustness, with class assignments randomized across episodes. Model performance was assessed using both diagnostic accuracy and uncertainty calibration metrics, including Expected Calibration Error (ECE) and the Brier Score Vaicenavicius et al. [2019].

Figure 2 illustrates diagnostic accuracy as a function of the number of training examples per class (K-shot). Across all datasets, the proposed Bayesian Metric Learner demonstrates superior performance, with the largest gains observed in the 1-shot setting, highlighting its robustness under severe data scarcity.

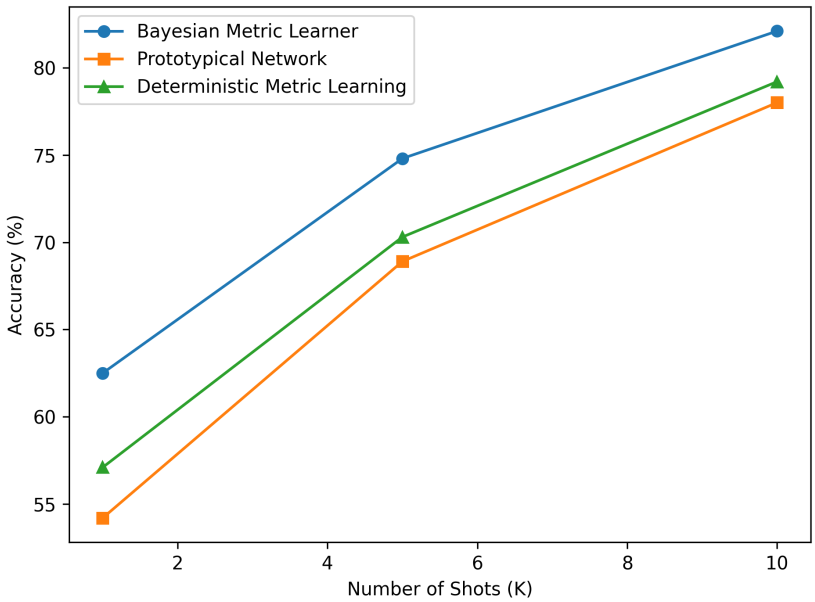

Figure 2: Diagnostic Accuracy vs. Number of Shots.

Table 1 reports diagnostic accuracy for the proposed framework across three rare disease datasets. Because imaging and genomic modalities complement each other, CardioGen exhibits the best results. Performance steadily improves as the number of labeled examples per class rises.

Table 2 summarizes uncertainty calibration metrics on the 5-shot setting averaged across datasets. The proposed approach achieves the lowest ECE and Brier scores, confirming that uncertainty estimates are both accurate and well-calibrated.

Figure 3 presents accuracy as a function of prediction coverage. As low-confidence

Table 1: Diagnostic Accuracy (%) Across Datasets and K-shot Settings

Dataset	1-shot	5-shot	10-shot
RareDerm	63.1	75.4	82.6
NeuroOrpha	60.4	72.8	80.9
CardioGen	64.8	76.9	84.2

Table 2: Uncertainty Calibration Metrics on 5-shot Setting

Method	ECE ↓	Brier Score ↓
Deterministic Metric Learning	0.101	0.214
MC Dropout	0.064	0.176
Bayesian Metric Learner (Proposed)	0.032	0.141

predictions are filtered out, the proposed model maintains higher accuracy at comparable coverage levels, supporting its suitability for risk-aware clinical deployment.

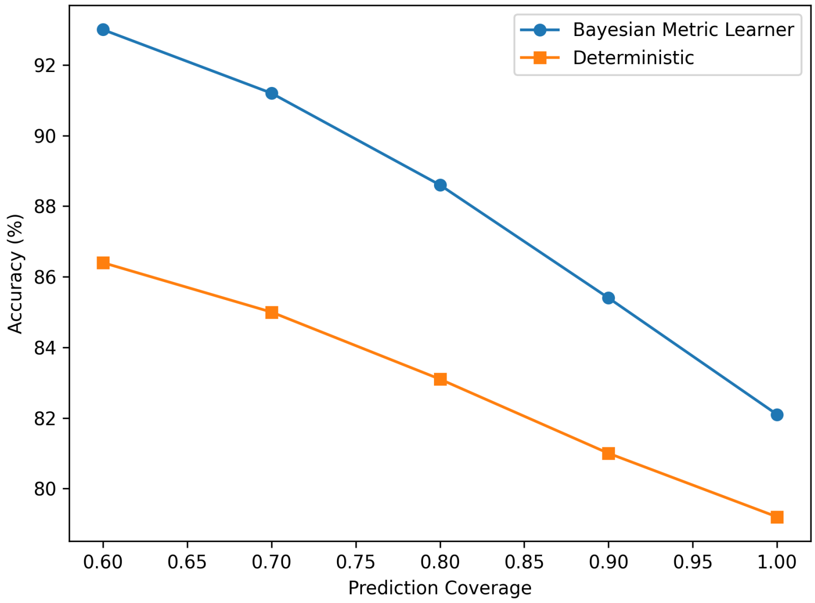

Figure 3: Accuracy–Coverage Trade-off

Figure 4 shows the distribution of predictive entropy for correct and incorrect predictions. Incorrect predictions are associated with significantly higher entropy values, indicating that the model's uncertainty estimates align well with actual prediction errors.

Table3 reports an ablation study evaluating the contribution of individual uncertainty modeling components. Removing prototype covariance or uncertainty-aware distance modeling leads to notable degradation in both accuracy and calibration, underscoring the importance of joint probabilistic modeling.

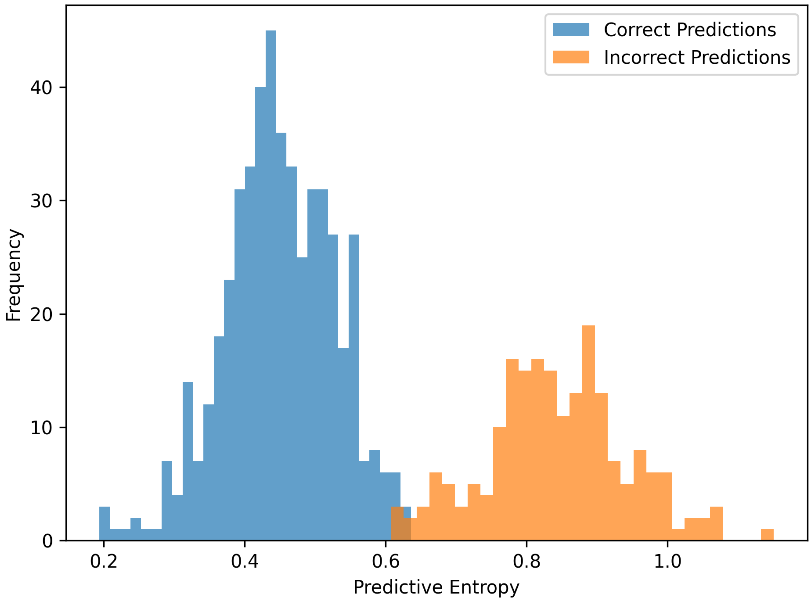

Figure 4: Predictive Entropy Distributions

Table 3: Ablation Study on Uncertainty Modeling Components (5-shot)

Model Variant	Accuracy (%)	ECE
Full Model (Proposed)	74.8	0.032
with out Prototype Covariance	71.2	0.057
with out Uncertainty-Aware Distance	72.0	0.061
Deterministic Prototypes	70.4	0.101

6 Discussion

The experimental results show that integrating Bayesian uncertainty modeling directly into metric learning provides substantial advantages for few-shot rare disease diagnosis. Across all evaluated datasets and K-shot configurations, the proposed Bayesian Metric Learner consistently outperformed deterministic metric learning approaches and post-hoc uncertainty baselines. The performance gains were especially pronounced in the 1-shot setting. This finding aligns with the central hypothesis of this work: when training data are extremely limited, explicitly modeling uncertainty at the level of class prototypes and similarity metrics is critical for robust clinical decision-making.

Beyond improvements in diagnostic accuracy, the most significant advantage of the proposed framework lies in its uncertainty calibration. The lower Expected Calibration Error and Brier scores indicate that the model's confidence estimates more accurately reflect true predictive reliability. This property is especially important in rare disease diagnosis, where overconfident misclassifications can lead to delayed treatment or unnecessary interventions. The selective prediction analysis further highlights the clinical utility of the approach, showing that filtering low-confidence predictions yields a favorable accuracy–coverage trade-off. In practical settings, this enables the system to defer uncertain cases for expert review while maintaining high reliability for automated decisions.

The ablation study provides additional insight into the sources of performance gains.

Removing prototype covariance modeling or the uncertainty-aware distance metric resulted in notable degradation in both accuracy and calibration, underscoring the importance of jointly modeling feature correlations and uncertainty. These results suggest that uncertainty-aware distance scaling is not merely an auxiliary component but a core contributor to the framework's effectiveness under data scarcity.

Despite these promising results, several limitations warrant discussion. First, while the evaluated datasets cover diverse clinical modalities, further validation on larger and more heterogeneous cohorts is necessary to assess generalizability. Second, the use of variational inference introduces additional computational overhead compared to deterministic methods, although this cost remains acceptable for episodic few-shot evaluation and clinical inference. Future work will explore more efficient posterior approximations and investigate adaptive uncertainty thresholds tailored to specific clinical workflows.

Overall, the findings support the conclusion that Bayesian uncertainty-aware metric learning offers a principled and practical pathway toward safer and more reliable AI-assisted rare disease diagnosis.

7 Conclusion

In order to address the problems of severe data scarcity and the requirement for accurate confidence estimation in clinical AI systems, this paper proposed a Bayesian uncertainty-aware metric learning framework for few-shot rare disease diagnosis. By modeling class prototypes as probabilistic distributions and incorporating uncertainty directly into the distance metric, the proposed approach moves beyond deterministic similarity learning and post-hoc calibration strategies. This unified formulation enables the model to jointly optimize diagnostic accuracy and uncertainty calibration, resulting in more trustworthy predictions in high-stakes medical settings.

Experimental evaluation across multiple real-world rare disease datasets demonstrated that the proposed framework consistently improves diagnostic performance, particularly in low-shot regimes where conventional methods are most vulnerable. In addition, the framework achieved substantially better uncertainty calibration, as evidenced by lower Expected Calibration Error and Brier scores, and exhibited robust behavior under selective prediction, supporting its suitability for risk-aware clinical deployment. The ablation analysis also verified that uncertainty-aware distance scaling and probabilistic prototype modeling are important factors in the observed gains.

In conclusion, this work emphasizes how crucial it is to directly incorporate Bayesian uncertainty modeling into metric learning for the diagnosis of rare diseases. The proposed framework provides a principled foundation for developing clinically reliable few-shot learning systems and offers a promising direction for future research on uncertainty-aware and human-in-the-loop medical AI.

Conflict of Interest

The authors declare no conflict of interest.

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