Unsupervised Representation Learning Meets Pseudo-Label Supervised Self-Distillation: A New Approach to Rare Disease Classification

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Abstract. Rare diseases are characterized by low prevalence and are often chronically debilitating or life-threatening. Imaging-based classification of rare diseases is challenging due to the severe shortage in training examples. Few-shot learning (FSL) methods tackle this challenge by extracting generalizable prior knowledge from a large base dataset of common diseases and normal controls, and transferring the knowledge to rare diseases. Yet, most existing methods require the base dataset to be labeled and do not make full use of the precious examples of the rare diseases. To this end, we propose in this work a novel hybrid approach to rare disease classification, featuring two key novelties targeted at the above drawbacks. First, we adopt the unsupervised representation learning (URL) based on self-supervising contrastive loss, whereby to eliminate the overhead in labeling the base dataset. Second, we integrate the URL with pseudo-label supervised classification for effective self-distillation of the knowledge about the rare diseases, composing a hybrid approach taking advantages of both unsupervised and (pseudo-) supervised learning on the base dataset. Experimental results on classification of rare skin lesions show that our hybrid approach substantially outperforms existing FSL methods (including those using fully supervised base dataset) for rare disease classification via effective integration of the URL and pseudo-label driven self-distillation, thus establishing a new state of the art.

Keywords: Rare disease classification · Unsupervised representation learning · Pseudo-label supervised self-distillation.

1 Introduction

Rare diseases are a significant public health issue and a challenge to healthcare. On aggregate, the number of people suffering from rare diseases worldwide is

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estimated over 400 million, and there are about 5000–7000 rare diseases—with 250 new ones appearing each year [27]. Patients with rare diseases face delayed diagnosis: 10% of patients spent 5–30 years to reach a final diagnosis. Besides, many rare diseases can be misdiagnosed. Therefore, image-based accurate and timely diagnosis of rare diseases can be of great clinical value. In recent years, deep learning (DL) methods have developed into the state of the art (SOTA) for image-based computer-aided diagnosis (CAD) of many diseases [13,19,24]. However, due to the limited number of patients for a specific rare disease, collecting sufficient data for well training of generic DL classification models can be practically difficult or even infeasible for rare diseases.

To cope with the scarcity of training samples, a machine learning paradigm called few-shot learning (FSL) has been proposed [17] and achieved remarkable advances in the natural image domain [5,14,25,31]. In FSL, generalizable prior knowledge is learned on a large dataset of base classes, and subsequently utilized to boost learning of previously unseen novel classes given limited samples (the target task). Earlier approaches [5,14,25,31] to FSL mostly resorted to the concept of meta-learning and involved complicated framework design and task construction. Recently, Tian et al. [29] showed that superior FSL performance could be achieved by simply learning a good representation on the base dataset using basic frameworks, followed by fitting a simple classifier to few examples of the novel classes. Additional performance boosts were achieved through self-distillation [6,8]. How to implement a similar self-distilling strategy on an unsupervised base dataset, though, is not obvious. On the other hand, we are aware of only few methods [34,12,18,21] for FSL of medical image classification, and to the best of our knowledge, all of them relied on heavy labeling of the base dataset, causing a great burden for practical applications. Lastly, the meta-learning process and the target task are often isolated in most existing FSL approaches, and the meta-learner has little knowledge about its end task. For natural images, this setting is consistent with the general purpose of pretraining a classifier that can be quickly adapted for diverse tasks. For the scenario we consider, however, known types of rare diseases are mostly fixed, and their recognition constitutes a definite task. We hypothesize that, by bridging the base dataset and the definite task, the performance can be boosted for the rare disease classification. In this regard, we consider this work a specific and practically meaningful application of the general FSL.

In this work, we propose a novel hybrid approach to rare disease classification, which combines unsupervised representation learning (URL) and pseudo-label supervised self-distillation [6,8]. Motivated by the recent surge of representation learning in FSL [2,29], we first build a simple yet effective baseline model based on URL, where a good representation is learned on a large unlabeled base dataset consisting of common diseases and normal controls (CDNC) using contrastive learning [7], and applied to rare disease classification. So far as we are aware of, this is the first study that explores few-shot medical image classification using an unsupervised base dataset. Then, we further propose to inject knowledge about the rare diseases into representation learning, to exploit the
CDNC data for a more targeted learning of the rare diseases. Specifically, we use the baseline model as a teacher model to generate pseudo labels for instances of CDNC belonging to the rare diseases, to supervise knowledge distillation to the student model. Our rationale is that CDNC and rare diseases often share common characteristics, thus we can steer the representation learning on the former towards characteristics that can better distinguish the latter via supervision by the pseudo labels. In addition, we empirically explore design options for the distillation, and find that a hybrid self-distillation integrating URL and pseudo-label supervised classification yields the best performance. Therefore, our main contributions are two folds: the novel application of URL to rare disease classification, and hybrid distillation combining contrastive and pseudo-label learning. Experimental results on the ISIC 2018 skin lesion classification dataset show that the URL-based baseline model already outperforms previous SOTA FSL methods (including those using fully supervised base dataset), and that further boosts in performance are achieved by the proposed hybrid approach.

2 Methods

Problem Setting. Similar to Li et al. [18], we formulate the task of rare disease classification as a few-shot learning (FSL) problem. Specifically, we model a specific task as \( T = \{S, Q\} \) consisting of a support set \( S = \{(x, y)\} \) and a query set \( Q = \{(x, y)\} \), where \( x \) is an image and \( y \) is its label. An \( N \)-way \( K \)-shot task includes \( N \) rare diseases, each with \( K \) instances in \( S \), where \( K \) is small. Thus \( y \in [1, \ldots, N] \) and \(|S| = N \times K\). The task instance \( T \) is randomly drawn from a distribution \( p(T) \), with \( S \) and \( Q \) randomly sampled from a dataset \( D_{\text{rare}} \) consisting of rare diseases. Only \( S \) is available for training and \( Q \) is solely for testing. In addition, there is a large base dataset \( D_{\text{base}} \) consisting of common diseases and normal controls (CDNC). The target is optimal classification performance on \( Q \).
given $S$ and $D_{\text{base}}$. In this work, we consider $D_{\text{base}}$ to be unlabeled for a more generally applicable approach in practice by eliminating the need for annotation.

**Method Overview.** An overview of our method is shown in Fig. 1. Given $D_{\text{base}}$, we first perform unsupervised representation learning (URL) to train the embedding function $f_q$ (Fig. 1(a)). Next, a simple classifier $f_c$ is appended to the learned $f_q$ (with frozen parameters) to compose a baseline model $F$ (Fig. 1(b)), where $f_c$ is optimized on $S$. Then, $F$ is employed to assign each CDNC instance in $D_{\text{base}}$ a pseudo label of the rare diseases (Fig. 1(c)). Lastly, a self-distillation via hybrid unsupervised and pseudo-label supervised representation learning is performed on $D_{\text{base}}$ to produce the final (student) model $F'$ (Fig. 1(d)).

**URL on CDNC for Rare Disease Classification.** Inspired by the recent success of representation learning in FSL [2,29] and based on the recent advances in URL [1,7], we propose to perform URL on the big yet unlabeled CDNC dataset for rare disease classification. Specifically, we adopt instance discrimination with the contrastive loss [7,20] as our self-supervising task. We employ MoCo_v1 [7], where each image $x_i$ in $D_{\text{base}}$ is augmented twice to obtain $x^q_i$ and $x^k_i$, whose embedded representations are subsequently obtained by $q_i = f_q(x^q_i; \theta_q)$ and $k_i = f_k(x^k_i; \theta_k)$, where $f_q$ and $f_k$ are the query and key encoders parameterized by $\theta_q$ and $\theta_k$, respectively. The contrastive loss $L_{\text{con}}$ is defined as [20]:

$$L_{\text{con}}(x_i) = -\log \left[ \frac{\exp (q_i \cdot k_i / \tau)}{\exp (q_i \cdot k_i / \tau) + \sum_{j=1}^L \exp (q_i \cdot k_j / \tau)} \right],$$

where $L$ is the number of keys stored in the dynamic dictionary implemented as a queue, $\tau$ is a temperature hyperparameter. Intuitively, this loss is the log loss of an $(L+1)$-way softmax-based classifier trained to discriminate the (augmented) instance $x_i$ from other images stored in the dictionary queue (represented by their embeddings). Then, $\theta_q$ is updated by back-propagation whereas $\theta_k$ is updated with a momentum $m$: $\theta_k \leftarrow m\theta_k + (1-m)\theta_q$, where $m \in [0,1)$. Another notable difference of our work from the prevailing meta-learning based approaches is that we randomly sample mini-batches of training images from $D_{\text{base}}$, instead of iteratively constructing episodic training tasks as in most previous works [18,28,26,14,10]. This back-to-basic training scheme has proven effective despite being simpler [29], especially for an unsupervised $D_{\text{base}}$ where category information is missing for episode construction.

After the URL, we freeze $\theta_q$ and append a simple classifier $f_c$ to $f_q$ to form a baseline model $F = f_c(f_q)$ for rare disease classification. Like [29], we use logistic regression for $f_c$, whose parameters $\theta_c$ are optimized on the support set $S$.

**Self-Distillation of Rare Disease Knowledge.** Despite its decent performance, the baseline model completely ignores the precious knowledge about target rare diseases contained in the support set $S$ during representation learning. We hypothesize that a better representation learning for classification of the
target rare diseases can be achieved by fully exploiting this knowledge while at
the same time utilizing the big unlabeled data in $D_{\text{base}}$. To do so, we propose to
inject target task knowledge extracted from $S$ into the representation learning
process via knowledge distillation [8], which can transfer knowledge embedded
in a teacher model to a student model. In addition, we adopt the born-again
strategy where the teacher and student models have an identical architecture,
for its superior performance demonstrated by Furlanello et al. [6].

The key idea behind our knowledge distillation scheme is that, although
$D_{\text{base}}$ and $D_{\text{rare}}$ comprise disjoint classes, it is common that certain imaging charac-
teristics (e.g., color, shape and/or texture) of the CDNC data are shared by
the rare diseases. Therefore, it is feasible to learn rare-disease-distinctive repre-
sentations and classifiers by training the networks to classify CDNC instances
as rare diseases of similar characteristics. Mathematically, we use the baseline
model $F$ as the teacher model to predict the probabilities of each image $x$ in
$D_{\text{base}}$ belonging to the rare diseases in $D_{\text{rare}}$: $p = F(x) = [p_1, \ldots, p_N]^T$, where
$\sum_{n=1}^{N} p_n = 1$. Next, we define the pseudo label $y = [y_1, \ldots, y_N]^T$ based on $p$
with two alternative strategies: (i) hard labeling where $y_n = 1$ if $n = \text{argmax}_n p_n$
and 0 otherwise, and (2) soft labeling where $y_n = p_n$. In effect, the first strategy
indicates the rare disease that $x$ resembles most, whereas the second reflects the
extents of resemblance between $x$ and all the rare diseases in $D_{\text{rare}}$. In addition,
we propose a hybrid distilling loss integrating pseudo-label supervised classi-
fication and contrastive instance discrimination. As we will show, the hybrid
distillation scheme is important for preventing overfitting to noise and bias in
the small support set. Then, adopting the born-again [6] strategy, a randomly
initialized student model $F' = f'_c(f'_q)$ parameterized by $\theta'_c$ and $\theta'_q$ is trained to
minimize the hybrid loss $L_{\text{dis}}$:

$$L_{\text{dis}} = L_{\text{con}}(x; \theta'_q, \theta'_k) + L_{\text{cls}}(y, F'(x; \theta'_q, \theta'_c)),$$

(2)

where $\theta'_k$ are parameters of the key encoder $f'_k$ (for computation of $L_{\text{con}}$) and
updated along with $\theta'_q$, and $L_{\text{cls}}$ is the pseudo-label supervised classification loss.
For $L_{\text{cls}}$, the cross-entropy and Kullback-Leibler divergence losses are used for
the hard and soft labels, respectively. Lastly, to allow for an end-to-end training,
a fully connected layer (followed by softmax) is used for $f'_c$.

After distillation, the student model $F' = f'_c(f'_q)$ can be directly used for rare
disease classification. One might argue for an alternative way of usage: discarding $f'_c$ but appending a logistic regression classifier fit to the support set to $f'_q$, just
like in the baseline model. However, as confirmed by our comparative experiment
(supplement Table S1), direct use of $F'$ performs much better. This is because,
the knowledge about the rare diseases is distilled into not only $f'_q$ but also $f'_c$, thus discarding the latter results in performance degradation. Lastly, through
preliminary experiments we find that distilling more than once does not bring
further improvement. Therefore, we perform the self-distillation only once.

**Adaptive Pseudo Labels.** In practice, the pseudo labels defined by $F$ may
not be entirely trustworthy, given the tiny size and potential noise and bias of
the support set. This may adversely affect performance of the student model. To alleviate the adverse effect, we further propose adaptive pseudo labels based on the self-adaptive training strategy. Concretely, given the prediction \( p' \) by the student model and pseudo labels \( y \) defined above, we combine them as our new training target: \( y_{\text{adpt}} = (1 - \alpha) \times y + \alpha \times p' \), where \( \alpha \) is a confidence parameter controlling how much we trust the teacher’s knowledge. \( y_{\text{adpt}} \) is termed adaptive hard/soft labels depending on \( y \) being hard or soft pseudo labels. Many previous works used a constant \( \alpha \) \[11,32\]. In the first few epochs, however, the student model lacks reliability—it gradually develops a better ability of rare disease classification as the training goes on. Therefore, we adopt a linear growth rate \[15\] for \( \alpha \) at the \( t \)th epoch: \( \alpha_t = \alpha_T \times (t/T) \), where \( \alpha_T \) is the last-epoch value and set to 0.7 as in \[15\], and \( T \) is the total number of epochs. As suggested by the comparative experiments (supplement Table S2), the adaptive hard labels work the best, thus are used in our full model for comparison with other methods.

3 Experiments

Dataset and Evaluation Protocol. The ISIC 2018 skin lesion classification dataset \[4,30\] includes 10,015 dermoscopic images from seven disease categories: melanocytic nevus (6,705), benign keratosis (1,099), melanoma (1,113), basal cell carcinoma (514), actinic keratosis (327), dermatofibroma (115), and vascular lesion (142). From that, we simulate the task of rare disease classification as below. Following Li et al. \[18\], we use the four classes with the most cases as the CDNC dataset \( D_{\text{base}} \), and the other three as the rare disease dataset \( D_{\text{rare}} \). \( K \) images are sampled for each class in \( D_{\text{rare}} \) to compose the support set \( S \) for a 3-way \( K \)-shot task. Compared to the binary classification tasks \[18\], the multi-way evaluation protocol more genuinely reflects the practical clinical need where more than two rare diseases are present, albeit more challenging. As to \( K \), we experiment with 1, 3, and 5 shots in this work. All remaining images in \( D_{\text{rare}} \) compose the query set \( Q \) for performance evaluation. Again, this task construction more genuinely reflects the intended scenario of rare disease classification—where only few examples are available for training a classifier to be applied to all future test cases—than the repeated construction of small \( Q \)'s \[18\]. We sample three random tasks \( T \sim p(T) \) and report the mean and standard deviation of these tasks. Besides accuracy, we additionally employ the F1 score as the evaluation metric considering the data imbalance between the rare disease classes.

Implementation. The PyTorch \[26\] framework (1.4.0) is used for experiments. We use the ResNet-12 \[16,29,22\] architecture as backbone network for \( f_q \) and \( f_k \), for its superior performance in the comparative experiments (supplement Table S3). We train the networks for 200 epochs with a mini-batch size of 16 images on 4 Tesla V100 GPUs. We adopt the stochastic gradient descent optimizer with a momentum of 0.9 and a weight decay of 0.0001. The learning rate is initialized

\[3\] https://challenge2018.isic-archive.com/task3/
Table 1. Evaluation results and comparison with SOTA FSL methods with ResNet-12 as backbone network. Data format: mean (standard deviation).

| Method                        | (N, K) = (3, 1)     |       | (N, K) = (3, 3)     |       | (N, K) = (3, 5)     |       |
|-------------------------------|---------------------|-------|---------------------|-------|---------------------|-------|
|                               | Accuracy (%)        | F1 score (%) | Accuracy (%)        | F1 score (%) | Accuracy (%)        | F1 score (%) |
| Training from scratch         | 37.74 (1.07)        | 29.90 (3.65) | 39.76 (0.88)        | 35.60 (1.72) | 45.36 (3.76)        | 38.41 (4.06)  |
| ⊥ SML-MAML [5]               | 47.49 (5.38)        | 42.33 (6.16) | 55.55 (3.12)        | 40.19 (1.20) | 58.94 (2.55)        | 55.51 (2.16)  |
| RelationNet [28]             | 46.10 (4.80)        | 39.98 (6.73) | 47.29 (2.77)        | 43.37 (3.65) | 55.71 (3.30)        | 49.34 (3.57)  |
| ProtoNets [25]               | 35.18 (3.12)        | 30.81 (3.09) | 38.59 (1.91)        | 33.11 (2.08) | 42.45 (2.45)        | 34.92 (3.70)  |
| DAML [18]                    | 50.05 (5.18)        | 41.65 (5.98) | 55.57 (3.55)        | 49.01 (6.62) | 59.44 (3.17)        | 54.66 (2.44)  |
| ⊥ UML-UMTRA [14]            | 57.88 (5.55)        | 51.61 (5.55) | 55.29 (3.34)        | 54.51 (3.50) | 57.53 (3.76)        | 54.55 (3.96)  |
| CACTUs-MAML [9]             | 42.98 (2.91)        | 35.38 (3.08) | 44.44 (3.35)        | 39.94 (3.65) | 48.11 (4.20)        | 44.32 (3.65)  |
| CACTUs-ProtoNets [9]         | 42.67 (2.43)        | 39.24 (2.72) | 45.00 (3.26)        | 39.69 (2.66) | 47.95 (3.52)        | 44.08 (2.63)  |
| ⊥ SRL-SRL-simple [29]        | 54.45 (5.82)        | 57.02 (6.54) | 61.34 (6.31)        | 57.85 (3.36) | 70.53 (2.77)        | 65.58 (3.72)  |
| SRL-distil [29]              | 55.43 (7.30)        | 51.18 (5.50) | 64.92 (6.69)        | 59.88 (4.87) | 72.78 (1.67)        | 65.89 (2.54)  |
| ⊥ URL-SimCLR [1]            | 52.47 (5.53)        | 47.06 (6.24) | 65.12 (3.76)        | 57.53 (5.57) | 76.18 (3.76)        | 62.73 (3.78)  |
| MoCo-v2 [3]                 | 59.95 (4.73)        | 55.98 (3.81) | 70.84 (2.91)        | 64.77 (3.69) | 75.80 (1.85)        | 70.69 (2.13)  |
| MoCo-v1 (baseline) [7]      | 61.90 (2.92)        | 56.30 (1.48) | 74.92 (2.96)        | 69.50 (5.72) | 79.01 (2.00)        | 74.47 (3.03)  |
| Hybrid distil (ours)         | 64.15 (2.86)        | 61.01 (1.30) | 75.82 (2.47)        | 73.34 (2.30) | 81.16 (2.60)        | 77.35 (4.21)  |

Comparison to SOTA Methods. According to the labeling status of the base dataset and genre of the methodologies, all the compared methods are grouped into four quadrants: (i) supervised meta-learning (SML) including MAML [5], Relation Networks [28], Prototypical Networks [25], and DAML [18], (ii) unsupervised meta-learning (UML) including UMTRA [14] and CACTUs [9], (iii) supervised representation learning (SRL; with or without self-distillation) [29], and (iv) URL including SimCLR [1], MoCo-v2 [3], MoCo-v1 [7] (composing the baseline model in our work), and our proposed method. These methods cover a wide range of the latest advances in FSL for image classification. For reference purpose, we also show the results of training a classifier from scratch solely on S. Besides the ResNet-12 backbone, we additionally show the results using the 4 conv blocks [31] as the backbone network considering its prevalent usage in the FSL literature [5,28,25,14,9]. Note that for all compared methods, we optimize their performance via empirical parameter tuning.

The results are shown in Table 1 (ResNet-12) and supplement Table S4 (4 conv blocks), on which we make the following observations. First, the representation learning based methods generally achieve better performance than the meta-learning based irrespective of the labeling status of $D_{base}$, which is consistent with the findings in the natural image domain [29]. Second, the URL based methods surprisingly outperform the SRL based in most circumstances. A possible explanation may be that the few classes in $D_{base}$ present limited vari-
ations and make the representations overfit to their differentiation, whereas the task of instance discrimination in URL forces the networks to learn more diverse representations that are more generalizable on novel classes. Especially, the baseline model presented in this work (URL with MoCo_v1 [7]) wins over the SRL plus self-distillation [29] by large margins. Third, our proposed hybrid approach brings further improvements upon the baseline model in both accuracy (∼1–2% with ResNet-12) and F1 score (∼3–5% with ResNet-12). Notably, it achieves an accuracy of 81.16% in the 5-shot setting without any label of the base dataset. These results strongly support our hypothesis that, by extracting the knowledge about the rare diseases from the small support set and injecting it into the representation learning process via pseudo-label supervision, we can fully exploit the large CDNC dataset to learn representations and classifiers that can better distinguish the rare diseases. To further investigate whether the improvements sustain higher $K$ values, we conduct extra experiments (with ResNet-12) for the baseline and hybrid models with $K = 10$ and $20$. The results confirm that our proposed hybrid approach still wins over the baseline model by ∼1% absolute differences in both metrics and settings, yielding the accuracies and F1 scores of 83.65% and 79.98% when $K = 10$, and of 86.91% and 83.40% when $K = 20$. Lastly, the results using ResNet-12 as backbone are generally better than those using the 4 conv blocks, as expected.

**Ablation Study.** We probe the effect of the proposed hybrid distillation by comparing performance of distilling with only $\mathcal{L}_{\text{cls}}$ and the full model. In addition, we experiment with a variant of $\mathcal{L}_{\text{dis}}$ where $\mathcal{L}_{\text{cls}}$ is replaced by an L1 loss $\mathcal{L}_{\text{reg}}$ to directly regress the output of $f_q$, to evaluate the effect of injecting knowledge about the rare diseases. Results (Table 2) show that distilling with $\mathcal{L}_{\text{cls}}$ alone brings moderate improvement upon the baseline model, suggesting the efficacy of injecting rare disease knowledge into representation learning. Yet, distilling with the proposed hybrid loss achieves further appreciable improvement. We conjecture this is because $\mathcal{L}_{\text{con}}$ helps avoid overfitting to the support set of the rare diseases, which may be affected by noise and bias due to its small size. On the other hand, distilling with $\mathcal{L}_{\text{reg}}$ (plus $\mathcal{L}_{\text{con}}$) gives performance similar to the baseline model, implying that it is the distilled knowledge about the rare diseases that matters, rather than the distillation procedure. These results confirm the efficacy of the hybrid distillation.

**Table 2.** Ablation study on the hybrid distillation (with ResNet-12 backbone and adaptive hard labels). Data format: mean (standard deviation).

| $\mathcal{L}_{\text{dis}}$ | $(N, K) = (3, 1)$ | $(N, K) = (3, 3)$ | $(N, K) = (3, 5)$ |
|--------------------------|------------------|------------------|------------------|
|                           | Accuracy (%)     | F1 score (%)     | Accuracy (%)     | F1 score (%)     | Accuracy (%)     | F1 score (%)     |
| N.A.                     | 61.90 (2.92)     | 56.30 (1.48)     | 74.92 (2.96)     | 69.50 (5.72)     | 79.01 (2.00)     | 74.47 (3.03)     |
| $\mathcal{L}_{\text{cls}}$ | 63.70 (3.39)   | 57.31 (7.73)     | 74.92 (2.10)     | 70.28 (3.97)     | 80.24 (1.61)     | 77.29 (2.91)     |
| $\mathcal{L}_{\text{con}} + \mathcal{L}_{\text{cls}}$ | **64.15** (2.86) | **61.01** (1.30) | **75.82** (2.47) | **73.34** (3.20) | **81.16** (2.60) | **77.35** (4.21) |
| $\mathcal{L}_{\text{con}} + \mathcal{L}_{\text{reg}}$ | 62.20 (5.18) | 56.19 (4.28) | 74.43 (2.88) | 69.74 (4.13) | 79.14 (2.09) | 74.41 (2.65) |
4 Conclusion

In this work, we proposed a novel approach to rare disease classification in two steps. First, we built a baseline model on unsupervised representation learning for a simple and label-free (w.r.t. the base dataset of common diseases and normal controls) framework, which achieved superior performance to existing FSL methods on skin lesion classification. Second, we further proposed to utilize the baseline model as the teacher model for a hybrid self-distillation integrating unsupervised contrastive learning and pseudo-label supervised classification. Experimental results suggested that the hybrid approach could effectively inject knowledge about the rare diseases into the representation learning process through the pseudo-labels, and meanwhile resist overfitting to noise and bias in the small support set thanks to the contrastive learning, and that it had set a new state of the art for rare disease classification.

Acknowledgments. This work was supported by the Fundamental Research Funds for the Central Universities (Grant No. 20720190012), Key-Area Research and Development Program of Guangdong Province, China (No. 2018B010111001), and Scientific and Technical Innovation 2030 - “New Generation Artificial Intelligence” Project (No. 2020AAA0104100).

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Supplementary Material: Unsupervised Representation Learning Meets Pseudo-Label Supervised Self-Distillation: A New Approach to Rare Disease Classification

Table S1. Performance comparison of alternative ways of applying the distilled student model (with ResNet-12 backbone and adaptive hard labels). “Direct” means directly using the student model $F' = f'_c(f'_q)$, and “LR” means replacing $f'_c$ with a logistic regression classifier fit to the support set. To validate that the difference in performance is not due to the exact type of the classifier, we also show the results of using a fully connected layer (FC) finetuned on the support set for the baseline model. Data format: mean (standard deviation).

| Method       | Classifier | $(N, K) = (3, 1)$ | Accuracy (%) | F1 score (%) | $(N, K) = (3, 3)$ | Accuracy (%) | F1 score (%) | $(N, K) = (3, 5)$ | Accuracy (%) | F1 score (%) |
|--------------|------------|-------------------|--------------|--------------|-------------------|--------------|--------------|-------------------|--------------|--------------|
| MoCo v1 [7]  | LR         | 61.90 (2.92)      | 56.30 (1.48) | 74.92 (2.96) | 69.50 (5.72)      | 79.01 (2.00) | 74.47 (3.93) |
| (baseline)   | FC         | 60.91 (2.19)      | 55.21 (1.26) | 74.16 (3.77) | 68.09 (7.15)      | 78.20 (3.37) | 74.39 (3.90) |
| Hybrid-distill (ours) | LR         | 62.86 (2.70)      | 56.79 (4.38) | 74.45 (2.59) | 71.41 (4.14)      | 80.55 (1.94) | 75.45 (1.62) |
|              | Direct     | 64.15 (2.86)      | 61.01 (1.30) | 75.82 (2.47) | 73.34 (2.30)      | 81.16 (2.60) | 77.35 (4.21) |

Table S2. Accuracy comparison of four alternative designs of the pseudo labels (with ResNet-12 as backbone network). Data format: mean (standard deviation).

| Pseudo label design | $(N, K) = (3, 1)$ | $(N, K) = (3, 3)$ | $(N, K) = (3, 5)$ |
|---------------------|-------------------|-------------------|-------------------|
|                     | Accuracy (%)      | F1 score (%)      | Accuracy (%)      | F1 score (%)      | Accuracy (%)      | F1 score (%)      |
| Soft                | 62.16 (4.23)      | 56.25 (4.30)      | 75.17 (3.19)      | 71.48 (2.92)      | 79.89 (2.46)      | 74.61 (4.88)      |
| Hard                | 63.68 (3.90)      | 58.69 (4.82)      | 75.70 (2.90)      | 71.75 (2.75)      | 79.76 (1.27)      | 75.68 (2.42)      |
| Adaptive soft       | 62.26 (3.01)      | 57.10 (4.12)      | 75.45 (2.39)      | 69.23 (4.26)      | 79.74 (1.64)      | 74.41 (3.51)      |
| Adaptive hard       | 64.15 (2.86)      | 61.01 (1.30)      | 75.82 (2.47)      | 73.34 (2.30)      | 81.16 (2.60)      | 77.35 (4.21)      |
Table S3. Performance comparison of the baseline model using different backbones. Data format: mean (standard deviation).

| Backbone          | (N, K) = (3, 1) | (N, K) = (3, 3) | (N, K) = (3, 5) |
|-------------------|-----------------|-----------------|-----------------|
|                   | Accuracy (%) | F1 score (%) | Accuracy (%) | F1 score (%) | Accuracy (%) | F1 score (%) |
| 4 conv blocks     | 53.36 (8.89) | 46.90 (6.34) | 67.48 (6.06) | 59.77 (3.80) | 69.94 (5.67) | 64.31 (3.15) |
| MoblieNet v2      | 52.03 (6.40) | 44.76 (4.90) | 57.21 (7.10) | 48.26 (5.83) | 61.92 (10.09) | 56.85 (7.33) |
| ShuffleNet        | 60.91 (2.19) | 55.71 (1.26) | 74.16 (3.77) | 69.59 (7.15) | 78.20 (3.37) | 75.39 (3.90) |
| ResNet-12         | 61.90 (2.92) | 56.30 (1.48) | 74.92 (2.96) | 69.50 (5.72) | 79.01 (2.00) | 74.47 (3.03) |
| ResNet-18         | 56.97 (1.15) | 48.27 (4.25) | 71.88 (4.83) | 65.35 (7.56) | 77.27 (4.01) | 71.80 (4.16) |
| ResNet-50         | 59.90 (1.60) | 48.08 (5.20) | 70.96 (1.74) | 63.10 (4.37) | 74.17 (1.99) | 68.66 (2.26) |
| DenseNet-121      | 50.26 (4.38) | 44.03 (4.74) | 67.71 (0.71) | 59.22 (3.08) | 71.53 (1.79) | 66.54 (1.89) |

Table S4. Evaluation results and comparison with SOTA FSL methods with the 4 conv blocks as backbone network. Data format: mean (standard deviation).

| Method            | (N, K) = (3, 1) | (N, K) = (3, 3) | (N, K) = (3, 5) |
|-------------------|-----------------|-----------------|-----------------|
|                   | Accuracy (%) | F1 score (%) | Accuracy (%) | F1 score (%) | Accuracy (%) | F1 score (%) |
| Training from scratch | 35.91 (4.11) | 30.11 (1.73) | 38.95 (4.03) | 33.24 (2.89) | 43.13 (5.50) | 37.57 (1.32) |
| ⊥SML MAML          | 36.20 (4.22) | 30.64 (2.53) | 31.56 (3.05) | 35.38 (2.26) | 45.73 (3.62) | 40.51 (2.68) |
| RelationNet        | 41.11 (4.72) | 36.47 (4.60) | 42.63 (4.57) | 38.49 (4.77) | 49.98 (5.81) | 42.86 (4.81) |
| ProtoNets          | 44.97 (1.69) | 38.31 (2.05) | 36.38 (1.91) | 31.65 (2.73) | 37.95 (2.98) | 34.04 (2.40) |
| DAML               | 46.70 (2.74) | 49.96 (5.11) | 53.91 (3.23) | 44.90 (6.22) | 56.11 (2.39) | 53.29 (2.42) |
| ⊥URL             | 54.15 (5.57) | 53.88 (0.26) | 53.76 (2.78) | 50.07 (3.25) | 54.16 (2.00) | 50.47 (7.56) |
| CACTUs-MAML        | 39.45 (3.42) | 32.09 (2.60) | 42.20 (2.47) | 38.70 (3.80) | 45.31 (1.69) | 39.96 (3.46) |
| CACTUs-ProtoNets   | 32.24 (2.12) | 29.69 (0.84) | 35.08 (1.70) | 30.95 (2.69) | 36.86 (1.95) | 32.76 (3.10) |
| ⊥URL             | 55.88 (5.57) | 57.97 (1.56) | 57.90 (3.48) | 55.36 (6.62) | 60.62 (2.34) | 53.98 (3.29) |
| SRL-distil       | 50.14 (3.74) | 43.76 (2.54) | 58.20 (4.15) | 52.24 (3.06) | 62.07 (5.11) | 58.71 (5.64) |
| ⊥URL             | 54.07 (3.04) | 56.07 (7.94) | 56.25 (1.38) | 55.32 (3.22) | 62.65 (3.25) | 61.78 (5.25) |
| MoCo v2           | 48.88 (8.31) | 44.45 (7.16) | 59.71 (2.54) | 52.68 (3.75) | 62.91 (2.04) | 57.43 (2.95) |
| MoCo v1 (baseline) | 53.36 (8.89) | 46.90 (6.34) | 67.48 (6.06) | 59.77 (5.86) | 69.94 (5.67) | 64.31 (3.15) |
| Hybrid distil (ours) | **54.72** (8.46) | **47.28** (4.45) | **69.14** (3.36) | **62.56** (5.84) | **70.26** (4.97) | **65.89** (4.60) |