Direct Uncertainty Prediction for Medical Second Opinions

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Abstract

A persistent challenge in the practice of medicine (and machine learning) is the disagreement of highly trained human experts on data instances, such as patient image scans. We study the application of machine learning to predict which instances are likely to give rise to maximal expert disagreement.

As necessitated by this, we develop predictors on datasets with noisy and scarce labels. Our central methodological finding is that direct prediction of a scalar uncertainty score performs better than the two-step process of (i) training a classifier (ii) using the classifier outputs to derive an uncertainty score. This is seen in both a synthetic setting whose parameters we can control, and a paradigmatic healthcare application involving multiple labels by medical domain experts. We evaluate these direct uncertainty models on a gold standard adjudicated set, where they accurately predict when an individual expert will disagree with an unknown ground truth. We explore the consequences for using these predictors to identify the need for a medical second opinion and a machine learning data curation application.

1 Introduction

In both the practice of machine learning and the practice of medicine, a significant challenge is presented by disagreements amongst human labels. Machine learning classification models are typically developed on large datasets with one-hot labels. These are collected \cite{15, 21} by assigning classification instances \(x_i\) to multiple human evaluators, yielding several (noisy) labels, \(y_{i}^{(1)}, y_{i}^{(2)}, \ldots\). Unsurprisingly, these \(y_{i}^{(j)}\) typically have disagreements amongst them and must be carefully aggregated to give a single target value.

This label disagreement challenge becomes a full-fledged clinical problem in the healthcare domain, where individual ‘labellers’ are now highly trained human experts, doctors, with labels corresponding to diagnoses. Despite this domain expertise, the disagreement issue remains fundamental \cite{2, 1, 5, 12}. We define this clinical problem as the medical second opinion problem. Patient cases are typically viewed by one expert, but some cases naturally give rise to significant variations of expert diagnoses \cite{17, 1}. As this expert disagreement arises from human judgement and bias, the instance \(x_i\) itself contains features that may give rise to an intrinsic level of disagreement in human evaluation, separate from uniform noise \cite{17}, or noise dependent on solely ground truth labels (diagnoses) \cite{16}.

This motivates applying machine learning to patient instances \(x_i\) to predict which cases are likely to give rise to the most disagreement. This predictor could then directly be deployed as a diagnostic aid, flagging cases that might require a second opinion. Aside from clinical applications, this predictor can also be applied in data labelling and aggregation applications in machine learning \cite{15}.

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More precisely, given a patient instance $x_i$, we would like to predict how much disagreement we are likely to see given a few (typically two to three) different doctor grades $y_i^{(1)}, y_i^{(2)}, \ldots$. Our central methodological finding is that in these circumstances, direct prediction of uncertainty performs better than the two-step process of (i) training a classifier (ii) using the classifier outputs to derive an uncertainty. The basic contrast is as shown in Figure 1 rather than estimating uncertainty as a post-processing step applied to a classifier for the labeling problem, we can do better by learning the uncertainty directly as a predicate of the instance $x_i$.

We demonstrate this phenomenon in two ways — both through a formal framework, and in the context of an application. In both cases we show that direct prediction of variation can lead to substantially better performance. Since the canonical setting for this question is one in which there is disagreement over the assignment of a label to an instance $x_i$, we first consider an abstract setting in which points $x_i$ are drawn from a mixture of distributions. The standard goal in this setting would be to label $x_i$ with the distribution in the mixture that produced it; the disagreement problem that we consider here corresponds to predicting the uncertainty in the label assigned to $x_i$. We show that for general settings of this problem, we can achieve higher performance on this disagreement task by predicting disagreement as a quantity directly, rather than first estimating a distribution over labels. The framework is clean enough that we are able to suggest general insights into the contrast between these approaches.

We then turn to the clinical medical second opinion problem, applying direct uncertainty prediction in a setting where in which multiple medical experts provide labels to individual instances [5]. We find that the phenomenon holds here as well, and observe significant performance improvements over methods that first attempt to perform classification. We evaluate our methods both in terms of the underlying disagreement, and in terms of adjudicated (gold standard) labels that arise from explicit interaction among labelers. Finally, we consider how these estimates of disagreement might help guide the allocation of labeling effort, by highlighting instances where additional labels are needed.

2 Direct Uncertainty Prediction

The central prediction problem, primarily motivated by determining the need for a medical second opinion [17, 15, 12, 9, 18] can be described as follows. We have a dataset $T$, consisting of instances $x_i$, each with (typically only two to three) noisy labels $y_i^{(1)}, y_i^{(2)}, \ldots$. For each $x_i$, we wish to predict how much disagreement there is in the noisy labels. A first approach to doing this is to (i) train a classifier on the $x_i$ (with labels that are either (a) one-hot, by first somehow averaging the $y_i^{(j)}$, or (b) histograms, the empirical distribution of the $y_i^{(j)}$) (ii) use the probability distribution output by the classifier to score the $x_i$ on the predicted disagreement. Alternatively, one can train a model to output a scalar predicted disagreement value directly from the $x_i$ — a direct uncertainty predictor.

Of course, this uncertainty predictor needs labels (based on the disagreement of the $y_i^{(j)}$) to be trained on. In Appendix Section we discuss in detail different measures of uncertainty/disagreement and their aptness for the problem. One simple method of uncertainty labelling that we find effective in both our main application and synthetic settings is to give each $x_i$ a label 0 if all the $y_i^{(j)}$ agree and 1 if there is a disagreement. This aggregator works well in the medical setting due to the noisiness and scarcity of labels (typically only two or three per case). Labelling $x_i$ with agree/disagree in this way also gives a natural way
| Model Type                              | Disagree AUC Two Labels | Disagree AUC Three Labels |
|----------------------------------------|-------------------------|---------------------------|
| Uncertainty Prediction via Classification | 91.4%                   | 97.8%                     |
| Direct Uncertainty Prediction           | 94.2%                   | 99.0%                     |

Table 1: We train a (1) classifier (on histogram labels), and (2) a direct uncertainty predictor (on a binary agree/disagree label) in the setting where data is drawn from a uniform mixture of Gaussian distributions. The noisy labels are drawn from the natural noise distribution, equation (**) below, that is induced over labels. We then use (1) and (2) to output a probability of disagreement. In (1) this is computed according to equation (*) below, and in (**) this is just the predicted output. These models are then evaluated by computing percentage AUC on a test set from the same distribution. In both the two noisy label and three noisy label cases, directly predicting disagreement outperforms classifier-derived uncertainty.

to use the output probabilities of a classifier as a predictor of disagreement. Given a classifier on $c$ classes, with class $n$ having a probability of $p_n$ for an instance $x$, the predicted probability of disagreement can be computed as

$$P(D_x) = 1 - \sum_{n=1}^{c} p_n^2$$

(\text{in words, the probability that two draws from this distribution are not equal}) where $D_x$ is the event that experts will disagree on $x$.

We find that direct uncertainty prediction performs comprehensively better in numerous settings (Tables 2, 3, 4) than first training a classifier and then predicting uncertainty. In particular, our results suggest the following underlying phenomena:

*When data instances have inherent features corresponding to human expert labeler uncertainty, and labels are scarce, directly predicting uncertainty leads to better performance than the two step process of (i) first learning a classifier (ii) using classifier outputs to estimate uncertainty.*

We first demonstrate this in a synthetic setting, where we can closely examine the underlying parameters of the generative model, before moving on to our main application in the next section. We assume our data-generating process $p$ consists of a uniform mixture of $n$ multidimensional Gaussian distributions $p_i$. For any datapoint $x$ sampled from $p$, we get a natural noise distribution over possible classes, which we use to generate multiple labels for each $x$ with:

$$P(y = i|x) = \frac{p_i(x|\mu_i, \sigma_i)}{\sum_{j=1}^{n} p_j(x|\mu_j, \sigma_j)}$$  (**)

Each of the Gaussians has a covariance matrix of form $\sigma_{\text{high}I}$ or $\sigma_{\text{low}I}$ corresponding to high/low variance respectively. The means of the Gaussians are also drawn from a distribution so that the means corresponding to the low variance Gaussians form one cluster, and those corresponding to the high variance Gaussians correspond to another cluster. (See Appendix for full details.) The result is that the data $x$ has meaningful signal about whether it is likely to be high or low variance.

Next, we train two types of models on this data: a disagreement model that directly predicts whether $x$ will have labels that agree or disagree, and a classification model that predicts the empirical histogram of grades for each $x$. We then evaluate both models on a test set: for unseen examples, the disagreement model outputs the probability of disagreement, and the predicted distribution of the classification model is used as in (*) to predict a disagreement probability. We then compute an AUC on the agree/disagree instances correctly predicted. Our results are shown in Table 4, demonstrating that direct uncertainty prediction performs significantly better than uncertainty prediction via classification.
3 Related Work

The challenges posed by expert disagreement is a longstanding one, and prior work has put forward several approaches to address some of these issues. Under the assumption that the noise distribution is conditionally independent of the data instance given the true label, [11, 16, 13] provide theoretical analysis along with algorithms to denoise the labels as training progresses. However, the conditional independence assumption does not hold in our setting (Section 4 Figure 2(c)). Other work relaxes this assumption by defining a domain specific generative model for how noise arises [10, 23, 19] with some methods using additional clean data to pretrain models to form a good prior for learning. Modeling uncertainty in the context of noisy data has also been looked at through Bayesian techniques [8], and (for different models) in the context of crowdsourcing by [22, 20]. A related line of work [3, 21] has looked at studying the per labeler error rates, which also requires the additional information of labeler ids, an assumption we relax. Most related is [4], where a multiheaded neural network is used to model different labelers. Surprisingly however, the best model is independent of image features, which is the source of signal in our experiments.

4 Medical Problem Setting

The main motivation for our method is the medical second opinion problem – correctly identifying patient cases $x_i$ that require additional expert opinions. Our main dataset consists of retinal fundal images [5], large (587 by 587) images of the interior of the eye. These can be used to diagnose a variety of eye diseases, such as diabetic retinopathy, diabetic macular edema, age-related macular degeneration, and more. Here we focus on diabetic retinopathy (DR), which is graded according to a 5-class scale: grade 1 corresponds to no DR, 2 to mild DR, 3 to moderate DR, 4 to severe DR and 5 to proliferative DR [2]. A key threshold is at grade 3: grades $\geq 3$ are referable DR (requiring specialist attention), and grades $< 3$ are non-referable DR. Clinically, the most costly mistake is falsely diagnosing a referable DR patient with non-referable DR, which may result in blindness.

To build an uncertainty predictor, we have access to a large dataset $T$, split into a $T_{train}/T_{test}$ of images and corresponding labels (DR grades). Images $x$ in $T$ typically have only very few noisy labels. The majority have only one label, and most other images have only two to three labels, Figure 2(a). These labels are also very noisy, as shown in Figure 2(b). If we sample 3 labels, less than 50% of the images have data with no disagreement, and 25% have labels with a significant disagreement (2 or more grades apart.)

Similar to the synthetic setting in Section 2, we use this dataset to train both a classifier (on histogram labels – empirical probability distribution of the noisy labels), and a direct uncertainty predictor (takes input $x$ and directly outputs a score $p$ of uncertainty/disagreement.)

There are many possibilities for aggregating the noisy labels $y_{i,j}$ to an uncertainty score. Clinically, the DR grades can be interpreted either as a continuous progression — from mild (grade 1) to proliferative (grade 5) — or as categorical classes as each grade has specific features associated with it, e.g. grade 2 always indicates microaneurysms, while a grade of 5 can refer to lesions or laser scars (from earlier treatments) [2]. We therefore use two main methods of computing an uncertainty value from the noisy labels $y_{i,j}$: (1) thresholded variance (2) binary 0/1 agree/disagree. The former treats the grades as a continuous progression, and the latter as a categorical variable. We describe both of these disagreement aggregators and other alternatives in Appendix Section 3.

As healthcare is an especially sensitive domain, with incorrect predictions having significant consequences, our main evaluation is not only on $T_{test}$, but a small, gold standard adjudicated evaluation set $A$. Each image in $A$ has many more labels per image (on average 20, Figure 2(a)), graded by specialists, with a much higher inter-doctor agreement rate (Figure 2(b)) of 70%. Crucially, images in $A$ also have a single adjudicated label [9], determined via discussion by a group of experts. The adjudicated grade is used as a proxy ground truth, and we evaluate our models on how well their uncertainty estimates can predict differences between this adjudicated grade and specialist opinions on $A$. This evaluation is as close as possible to the core question of interest:
Figure 2: Statistics on our datasets $T$ and $A$, used for train/test and evaluation respectively. (a) $T$ has far fewer labels per image, with most images (~65%) only having 1 grade. (b) Label disagreement is also much higher in $T$; for images with 3 or more labels, over 50% have some disagreement, and 25% have high disagreement (two labels differ by more than 1 grade.) In comparison $A$ has 70% agreement and only 10% high disagreement. (c) Images with the same adjudicated label often have very different individual label distributions – the noisy label distribution depends critically on both the example and the ‘ground truth’.

Can we correctly identify patients where a single (or average) doctor diagnosis is mostly likely to disagree with the unknown ground truth condition?

This evaluation has the additional benefit of testing how robust the predictions are to distribution shifts – note that $A$ and $T$ have significantly different data statistics, Figure 2(b).

In the next sections, we develop, evaluate and apply direct uncertainty predictors as follows:

1. We split $T$ into $T_{train}, T_{test}$ and train a (i) classifier and (ii) a direct uncertainty predictor on $T_{train}$. We evaluate how well both of these can predict uncertainty on $T_{test}$, finding significant improvements with direct uncertainty prediction.

2. We evaluate the model uncertainty predictions on the adjudicated set $A$, seeing how well predicted uncertainty corresponds to disagreement between the adjudicated grade and (multiple different aggregations of) individual specialist grades. Direct uncertainty prediction again performs best, and the high AUC scores support the application to medical second opinions.

3. In clinical settings, raw classification is often less useful than a ranking [7], which enables varying amounts of effort allocation. We therefore evaluate ranking by model predicted uncertainty using Spearman’s rank correlation to see how well this matches to ranking by true difference between individual grades and the adjudicated grade. Direct uncertainty predictors again perform best.

4. Finally we look at an application to machine learning, using the uncertainty estimates of our models to determine how to budget labels, and see large improvements over a baseline of uniform budgeting.
| Task                  | Model Type                        | Performance |
|----------------------|-----------------------------------|-------------|
| Variance Prediction  | Histogram-E2E (Baseline)          | 70.6%       |
| Variance Prediction  | Histogram-PC (Strengthened Baseline) | 70.6%       |
| Variance Prediction  | Variance-E2E                      | 72.9%       |
| Variance Prediction  | Variance-E2E-2H                   | 72.7%       |
| Variance Prediction  | Variance-P                        | 74.4%       |
| Variance Prediction  | Variance-PR                       | 74.6%       |
| Variance Prediction  | Variance-PRC                      | 74.8%       |
| Variance Prediction  | Variance-LR                       | 72.4%       |
| Variance Prediction  | Disagree-PC                       | 73.3%       |
| Disagreement Prediction | Histogram-E2E (Baseline)       | 73.4%       |
| Disagreement Prediction | Histogram-PC (Strengthened Baseline) | 76.0%       |
| Disagreement Prediction | Disagree-P                      | 78.1%       |
| Disagreement Prediction | Disagree-PC                      | 78.1%       |
| Disagreement Prediction | Disagree-LR                      | 75.9%       |
| Disagreement Prediction | Variance-PRC                     | 77.3%       |

Table 2: Performance (Percentage AUC) averaged over three runs for models on Variance and Disagreement prediction tasks. In both settings, direct uncertainty models (Variance-, Disagree-) outperform classifier-based models (Histogram-).

5 First Experimental Results

We first train (1) classifiers (with histogram labels) and (2) direct uncertainty predictors (on variance/disagreement, Appendix Section B) on a train/test split of $T$, $T_{train}$, $T_{test}$. Our results (percentage AUC, averaged over three runs) are shown in Figure 2. Models are prefixed with their training targets, so Histogram- models correspond to baselines, while Variance-, Disagree- models correspond to direct uncertainty predictions. We find that the direct uncertainty predictors perform significantly better.

Baseline Model: Histogram-E2E Our baseline model is the convolutional neural network model used in [5] which is at its core an Inception-v3 model.

Variance-E2E and Variance-E2E-2H An analogous version of Histogram-E2E is Variance-E2E, which is the same architecture trained end to end on variance. However, as most datapoints in $T_{train}$ only have one label (Figure 2(a)), this significantly reduces the amount of data available to train the model and inspires the (-P) models below. (See Appendix for details of a variant, Variance-E2E-2H.)

Training from the Penultimate Layer (-P) The lack of data with multiple labels makes it challenging to train large models end to end on uncertainty, so we instead try training a smaller network from the penultimate layer: we take a pretrained model on DR classification, remove the final fully connected layer and then add a small neural network on top of this (typically with two hidden layers). This method also improves the baseline results. However, the strengthened baseline trained in this way (Histogram-PC) is still beaten in performance by all corresponding direct uncertainty prediction models (Variance-P, Variance-PR, Variance-PRC, Disagree-P, Disagree-PC).

Adding Calibration (-C) Informed by the work of [6], we try out a calibration technique based on a temperature parameter $T$, temperature scaling – see Appendix for details. This mostly further strengthens the baseline.
| Model Type          | Majority | Median | Majority = 1 | Median = 1 | Referable |
|---------------------|----------|--------|--------------|------------|-----------|
| Histogram-E2E-Var   | 78.1%    | 78.2%  | 81.3%        | 78.1%      | 85.5%     |
| Histogram-E2E-Disagree | 78.5%  | 78.5%  | 80.5%        | 77.0%      | 84.2%     |
| Histogram-PC-Var    | 77.9%    | 78.0%  | 80.2%        | 77.7%      | 85.0%     |
| Histogram-PC-Disagree | 79.0%  | 78.9%  | 80.8%        | 79.2%      | 84.8%     |
| Variance-PR         | 80.0%    | 79.9%  | 83.1%        | 80.5%      | 85.9%     |
| Variance-PRC        | 79.8%    | 79.7%  | 82.7%        | 80.2%      | 85.9%     |
| Disagree-P          | 81.0%    | 80.8%  | **84.6%**    | 81.9%      | **86.2%** |
| Disagree-PC         | 80.9%    | **80.9%** | 84.5%    | 81.8%      | **86.2%** |

Table 3: Evaluating models (percentage AUC) on predicting agreement between the adjudicated label and averages (majority/median/referable) of individual labels. All direct uncertainty models (Variance-, Disagree-) outperform all classifier-based models (Histogram-) on all tasks.

**Regression head (-R)** We also try adding a regression head to regularize the variance model, which gives a small improvement, more details in Appendix.

**Do we need the Penultimate layer? Training on Logits (-L)** We also evaluated the importance of training on the latent model representation (the prelogit layer) compared to directly trying to train the logit layer of the model, which did not work nearly as well, more details and insights in Appendix.

In summary, despite also comparing to strengthened variants of the baseline with prelogit finetuning and calibration (Histogram-PC), we find that directly predicting uncertainty achieves noticeably better performance reliably (across all model comparisons and tasks.)

6 Adjudicated Evaluation: Disagreement, Ranking, Budgeting

We now evaluate the models trained in Section 5 on our adjudicated dataset A, described in Section 4. We study how well our model uncertainty predictions can capture disagreements between the average individual doctor grade and the adjudicated grade, a proxy for the unknown ground truth condition. The strong performance in this task makes these predictors directly applicable to the medical second opinion problem. We also investigate the rank correlation between ranking by predicted disagreement and true disagreement (useful for variable effort allocation in clinical settings [7]), and a label budgeting application for machine learning data curation.

We first investigate whether we can use our model uncertainty prediction outputs to identify datapoints in A where the average individual doctor grades have minimal/maximal disagreement with the adjudicated grade. To do so, we consider two aggregation methods for the individual labels: the mode (termed the ‘majority vote’, also used in [5]), and the median. Our results are shown in Table 3. We explicitly define Histogram-PC-Var and Histogram-PC-Disagree to be strengthened baselines with outputs used to compute predicted variance and predicted disagreement respectively (similarly for Histogram-E2E-Var).

We also consider specific subcases of interest. First, the cases when Majority = 1 and Median = 1 are interesting: since 1 is the grade indicating a judgment of no DR, these are instances where most of the individual specialists have missed the onset of the condition. Second, there is a natural distinction between grades 3, 4, and 5 (which are referable for further action) and grades 1 and 2 (non-referable). We thus study this binary problem of determining whether an instance is referable. Again, we see that all direct uncertainty predictors beat the baselines (vanilla and strengthened) on all tasks (Table 3).

**Applying the Wasserstein distance.** The majority and median methods of aggregation are relatively insensitive to the individual grades. We thus also consider an aggregation measure that is more sensitively dependent on each individual grade, and more directly uses the continuous interpretation of the grades’ one-dimensional embedding.
Table 4: Evaluating Spearman’s correlation between ranking by model uncertainty and ranking by true Wasserstein distance between distribution of individual grades and the adjudicated grade. Like in Table 3 all direct uncertainty models beat all classification-based models on all settings. We also compare with correlation given by a varying number of human doctors. Our models are equivalent in this setting to having 5 grades.

For this purpose, we compute the Wasserstein distance between the distribution of all individual doctor grades and the adjudicated grade (treated as a point-mass distribution). We give background on the Wasserstein distance in the supplementary material; roughly speaking, for an underlying metric $d(\cdot, \cdot)$ (the distance on labels in our case), it defines the distance $\|f - g\|_W$ between distributions $f$ and $g$ to be the minimum cost (under $d$) to move the mass in distribution $f$ so that it is matches the mass in distribution $g$.

For our purposes, we let $\hat{q}(\cdot | x)$ be the empirical label distribution defined by the individual doctor grades for $x$, and $a(\cdot | x)$ the point mass distribution corresponding to the adjudicated grade. We show

**Theorem 1** If $f, g$ are (discrete) probability distributions and $g$ is a point mass distribution at $t_0$, then $\pi \in \Pi(f, g)$ is:

$$
\pi(r, t) = \begin{cases} 
0 & \text{if } t \neq t_0 \\
f(r) & \text{if } t = t_0
\end{cases}
$$

and apply this as $a(y_0 | x) = 1$ is a point-mass, to obtain $\|\hat{q}(\cdot | x) - a(\cdot | x)\|_W = \sum_{i=1}^5 d(i, y_0) \hat{q}(i | x)$. We consider three distances $d(\cdot, \cdot)$ on grades: the absolute value of the difference; an $L_2$ norm; and a 0-1 binary disagreement metric. (Further details are in the supplementary information.)

Using Spearman’s rank correlation coefficient, we compare how similar the ranking of instances by the Wasserstein distance is to the ranking using our uncertainty estimates. In Table 4 we see that over all metrics used, all direct uncertainty prediction models beat classifier based uncertainty models.

There is a natural scale against which to evaluate the performance of the rankings based on our uncertainty estimates: as a baseline we can compute the variance in each instance induced by the labels of only $n$ of the doctors, for $n \in \{2, 3, 4, 5, 6\}$, and ask how well the rankings according to these small sets of doctor labels compare to the Wasserstein ranking under Spearman’s rank correlation. In other words, how many doctor opinions would be required to match our ranking by estimated uncertainty? This comparison gives us a clean way to interpret our models – the best direct uncertainty models are as good in this setting as having 5 doctor labels.

**Budgeting Labels** We now consider one final task — budgeting labels. Unlike the previous tasks, which have been motivated by applications in medicine (determining which cases require a medical second opinion), this looks at data curation in machine learning. Suppose we start with a set of images with one label each,
but have a budget $B$ of additional labels we can get for the images. (In the Appendix, we demonstrate why multiple noisy labels for each image is crucial over more images with a single label each.) We’d like to know which images to assign the extra grades to, to ensure the aggregated individual grades are as close as possible to the adjudicated (ground truth) grades. Intuitively, we would like to allocate extra grades to the images for which there is the most uncertainty, which we can estimate with our model prediction. For our evaluation of this task, we focus on the subset of images that are referable (label $\geq 3$) according to the adjudicated grade.

We study this question by first drawing one grade for each image in $A$ to be the initial grade, and then determining (either randomly or using our model rankings) a subset of images to get another grade, which is drawn randomly from the remaining grades. (We allow at most one additional grade per image, and consider the case in which the budget $B$ is less than the total number of images; it is also interesting to consider cases with a higher budget and the freedom to determine how many additional labels each image gets.) Our results (percentage accuracy), are shown in Table 5. For full details of the method (very similar to our evaluation in Table 3), see the Appendix. One challenge we face in this setting is that the number of instances in $A$ with referable adjudicated grade is small. This, along with the process of only drawing one or two grades per image introduces a large amount of variance (an order of magnitude higher than for our other results), and so we explicitly show the variance in the performance in the table. While this makes it difficult to draw clear conclusions on the advantage of any one uncertainty model over another, it is clear that any allocation of labels based on an uncertainty ranking arising from model predictions vastly outperforms a naive uniform allocation of labels.

7 Discussion

In this paper, we apply machine learning to predict data instances giving rise to the most human expert disagreement. The core motivation and results for this prediction task are in the medical domain, where some patient cases have features resulting in high disagreement. These cases stand to gain significantly from medical second opinions. We demonstrate that in this setting, direct uncertainty prediction, which maps the data instance directly to an uncertainty value, performs consistently better than uncertainty prediction via classification. We rigorously evaluate these models on an adjudicated set, which illustrates that direct uncertainty predictors can accurately determine when individual doctors will disagree with an unknown ground truth condition. Besides the immediate clinical application for medical second opinions, such a predictor can also be used in machine learning settings, for data curation and label budgeting. Future work might look at mathematically characterizing the conditions where direct uncertainty estimation is most helpful, transferring these techniques to different data modalities, and extending the applications to machine learning data denoising.
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| Model Type       | $T_{test}$ AUC | Majority | Median | Majority= 1 | Median= 1 | Referable |
|------------------|----------------|----------|--------|-------------|-----------|-----------|
| Disagree Label Count | 76.3%         | 79.0%    | 78.7%  | 81.6%       | 79.0%     | 84.7%     |
| Disagree-P       | 78.1%         | 81.0%    | 80.8%  | 84.6%       | 81.9%     | 86.2%     |
| Disagree-PC      | 78.1%         | 80.9%    | 80.9%  | 84.5%       | 81.8%     | 86.2%     |

Table 6: Using label counts for disagreement prediction does not help in performance (AUC). Holdout AUC column corresponds to Disagreement Prediction Performance in Table 2, other columns refer to Table 3 in main text.

**Supplementary material for “Direct Uncertainty Prediction with Applications to Healthcare”**

### A Details on Synthetic Data

For the synthetic dataset, we generated 10000 train data points and 2000 test data points form a uniform mixture of fifteen 20-dimensional Gaussian distributions. The means of the distributions were drawn so that they formed two clusters: one cluster with variance 2 (the high variance cluster), and the other cluster with variance 0.0001 (the low variance cluster). This ensured that instances $x$ drawn from the clusters encoded information on whether they were high/low disagreement datapoints. There were 8 centers of high variance and 7 centers of low variance. The centers of high variance were drawn from a normal distribution with mean 0, variance $0.1/\sqrt{20}$ (with 20 being the number of dimensions) around the vector $[0, 1.5, 0, 0, \cdots 0]$ and the centers of low variance were drawn with the same distribution around $[1.5, 0, 0, \cdots 0]$.

### B Details of setting up Uncertainty Prediction

To train a direct uncertainty predictor, we need a label that indicates the (empirical) uncertainty of instances $x$. Recall from Section 4 that the DR grades can be interpreted either as (1) a continuous progression — from mild (grade 1) to proliferative (grade 5) — or as (2) categorical classes as each grade has specific features associated with it, e.g. grade 2 always indicates microaneurysms, while a grade of 5 can refer to lesions or laser scars [2].

To capture (1), we look at taking the variance of the observed empirical grades, which attributes higher uncertainty to large magnitude differences in grade values. However, training an uncertainty predictor via regression on the raw variance value does not work well in practice due to the mean square error loss getting influenced by outliers. Therefore, we truncate the variance into a binary 0/1 low/high variance label. We choose the threshold to be 2/9, the variance value resulting from an off by one grade disagreement on an image with three grades.

To capture (2), we simply give a 0/1 label based on whether all the noisy grades agree or there is at least one disagreement. This aggregation function seems extremely simple, but works well for a couple of reasons. Firstly, the scarcity of the labels (most images have two or three labels) means that we don’t have to explicitly weight the 0/1 by the total number of grades (i.e. disagree number is pairs that disagree divided by total pairs of grades.) In fact, as shown in Table 6, weighting explicitly by number of grades decreases performance, likely because the task becomes more like a regression than a classification.

Both of these uncertainty labels also have clear baselines using the outputs of the classifier – if the classifier probability output for class $i$ is $\hat{p}_i$, we can estimate the predicted variance with $\sum_{n=1}^{5} n^2 \hat{p}_n - \left(\sum_{n=1}^{5} n\hat{p}_n\right)^2$, and probability of disagreement with $1 - \sum_{n=1}^{5} \hat{p}_n^2$.

### C Additional Model Details

**Variance-E2E** We try a variant of Variance-E2E, Variance-E2E-2H, which has one head for predicting variance and the other for classifying, to enable usage of all the data. We then evaluate the variance head on $T_{test}$, but in fact notice a small drop in performance.
Details on Calibration Via Temperature Scaling We set the predictions of the model to be $f(F/T)$ where $f$ is the softmax function, applied pointwise, and $F$ are the logits. We initialize $T$ to 1, and then split $T_{train}$ into a $T'_{train}$ and a $T'_{valid}$. We train as normal on $T'_{train}$, with $T$ fixed at 1, and then train on $T'_{valid}$ by only varying the temperature $T$, and holding all other parameters fixed.

Regression for Variance Prediction Model We also consider a two head variance prediction model, where one head predicts a thresholded variance value like before, while the other head does regression on the numerical variance value. We evaluate on the thresholded variance head as usual. Note that only doing regression on the variance value fails at being a good uncertainty predictor, likely due to the poor scaling (some values with very high variance distorting mean squared error.)

Do we need the penultimate layer? We tried seeing if we could match performance by training on the model logits instead of the representation at the hidden (penultimate) layer. WE found that while this improved on the baseline results, it did not match the performance from training on the latent representation. (We also controlled for parameter difference by adding additional hidden layers but this did not lead to improvements.) This suggests that some information is lost between the prelogit and logit layers.

D Background on the Wasserstein Distance

Given two probability distributions $f, g$, and letting $\Pi(f, g)$ be all product probability distributions with marginals $f, g$, the Wasserstein distance between $p, q$ is

$$||f - g||_W = \inf_{\pi \in \Pi(f,g)} \mathbb{E}_{(r,t) \sim \pi} [d(r, t)]$$

where $d(\cdot, \cdot)$ is some metric. This distance has connections to optimal transport, and corresponds to the cost of (with respect to $d(\cdot, \cdot)$) moving the mass in distribution $f$ so that it is matches the mass in distribution $g$ as efficiently as possible. We can represent the amount of mass to move from $r$ to $t$ with $\pi(r, t)$; and be consistent with the mass at the start, $f(r)$, and the mass at the end $g(t)$ we must have that $\int_r \pi(r, t') = f(r)$ and $\int_t \pi(r', t) = g(t)$.

In our setting we let $\hat{q}(\cdot|x)$ be the empirical probability distribution over labels defined by the individual doctor grades for a datapoint $x$, and $a(\cdot|x)$ the point mass distribution corresponding to the adjudicated grade. We wish to compute $||\hat{q}(\cdot|x) - a(\cdot|x)||_W$ for each $x$, which is simplified by $a(\cdot|x)$ being a point mass

In the main text, we asserted the following

**Theorem.** If $f, g$ are (discrete) probability distributions and $g$ is a point mass distribution at $t_0$, then $\pi \in \Pi(f, g)$ is:

$$\pi(r, t) = \begin{cases} 0 & \text{if } t \neq t_0 \\ f(r) & \text{if } t = t_0 \end{cases}$$

The proof is direct: for $t \neq t_0$, we must have $\int_r \pi(r', t) = g(t) = 0$, and so $\int_r \pi(r, t') = \pi(r, t_0) = f(r)$. Thus, in our setting, letting $a(y_0|x) = 1$, we have

$$||\hat{q}(\cdot|x) - a(\cdot|x)||_W = \sum_{i=1}^5 d(i, y_0)\hat{q}(i|x)$$

We consider three different cost metrics $d(\cdot, \cdot)$, each emphasizing different properties:

1. **Absolute Value** $d(r, t) = |r - t|$. This follows an interpretation in which the grades are equally spaced, so that all successive grade differences have the same weight.

2. **2-Wasserstein Distance** $d(r, t) = (r - t)^2$, and, to make into a metric

$$||\hat{q}(\cdot|x) - a(\cdot|x)||_W = \left( \sum_{i=1}^5 (i - y_0)^2\hat{q}(i|x) \right)^{1/2}$$

This adds a higher penalty for larger grade differences.
3 Binary Disagreement We set \( d(r, t) = 0 \) if \( r = t \) and 1 otherwise.

Having computed the Wasserstein distance, obtaining a real-valued level of difference between the individual values and the adjudicated grade for each instance, we look at how well the ranking of instances by this distance correspond to a ranking using our uncertainty estimates. We do this using Spearman’s rank correlation coefficient, a standard nonparametric measure producing a number in the interval \([-1, 1]\) that represents how well the relationship between two ranked variables can be represented by a monotonic function. Specifically, we first rank the images \( x \) by Wasserstein distance, and then rank again by the uncertainty prediction of different models. We then apply Spearman’s rank correlation to determine how monotonic this relationship is.

E Details On Budgeting

We evaluate the budgeting results by first binarizing the individual grades into referable/non-referable. If there is only a single grade, we directly check for agreement with the binarized adjudicated grade. If there are two grades, we label the image referable if at least one of the individual grades is referable. We then again check for agreement with the binarized adjudicated grade. This is consistent with the style of evaluation used in Table 3 in the referable column evaluation.

Note that one natural question arising from the budgeting scenario is whether it makes sense to have more data that is more noisily labelled, or less data with more noisy labels. If the labels have a bias to them, as is the case in the medical setting (doctors are more likely to grade an image with a lower grade than a higher grade), it is crucial to have multiple labels. To see this, we can train a model with all the data but only one label per datapoint (M1) and a model on half the data with more labels (M2) to diagnose DR. We then test to see if the model could correctly (according to adjudicated grade) distinguish two clinically relevant binary cases (i) [grade < 3, grade ≥ 3] (ii) [grade < 4, grade ≥ 4] AUCs for M1 were 97.1% and 91.5% while AUCs for M2 were 97.6% and 97.1% – i.e. M2 (more labels, less data) did better in both cases.