Simpler predictive models provide higher accuracy for ovarian cancer detection

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Abstract

Ovarian cancer remains a danger to women's health, and accurate screening tests would likely increase survival. Two established protein biomarkers, CA125 and HE4, have been shown to work well in isolation, but achieve even higher accuracy when combined using logistic regression (LR). We show here that this LR-based combination of protein concentrations achieves high accuracy when distinguishing healthy samples from cancer samples (AUC = 0.99) and benign masses from cancer (AUC = 0.86). This approach exhibits superior performance on an external validation cohort compared to a more complex method, which was published with the dataset we use here and tested on the same data. Our results are in line with the principle that simpler machine learning models will tend to exhibit better generalizability on new data.

Introduction

The American Cancer Society estimates that in 2024, the United States will see 19,680 new cases of ovarian cancer, and 12,740 women will die due to ovarian cancer [1]. Ovarian cancer is often diagnosed at advanced stages, when the prognosis is generally poorer than when found at an earlier stage [2]. For these reasons, accurate assays to detect ovarian cancer earlier are important to increase survival rates. These assays could be used in both a screening setting, where asymptomatic individuals are tested for the presence of cancer, and in a diagnostic context, where an individual with a known ovarian mass is tested to determine the likelihood that the mass is malignant.

For diagnosis of ovarian cancer, two common biomarkers used are the CA125 and HE4 proteins [2]. Elevated concentrations of each protein have been found to be associated with ovarian cancer [3,4], although HE4 also increases with age [5]. While each protein can act as a biomarker in its own right, researchers have also found ways to combine them to create a more accurate cancer detection algorithm. In 2009, Moore, et al. presented a logistic regression (LR)

approach, the Risk of Ovarian Malignancy Algorithm (ROMA), which combined the two values to achieve greater diagnostic accuracy than either protein alone [6]. ROMA uses the menopausal status of a patient to decide which LR model to use; in contrast, the Copenhagen Index [7] uses the patient's age along with the CA125 and HE4 serum levels in an LR model to arrive at its predicted probability of cancer.

Other cancer detection approaches have sought to address both screening and diagnostic scenarios. DELFI [8,9] is an algorithm that analyzes fragmentation patterns seen through sequencing of cell-free DNA (cfDNA) along with copy number information to detect cancer. Recently, Medina, et al. introduced their method DELFI-Pro [10], a computational pipeline using LR that combines CA125 and HE4 measurements with many of DELFI's cfDNA-derived features. For the detection of ovarian cancer, the authors show DELFI-Pro outperforms both the CA125 and the HE4 protein concentration levels. The authors also reported that the two proteins had the coefficients with the highest magnitude in their screening model, with the two proteins combined representing 68.8% of the total feature importance.

An important consideration in using machine learning models such as LR is to ensure that the size of the feature set is minimal while still providing adequate performance [11]. As recently stated by Divasón, et al. [12]: "A model that has good accuracy and low complexity, i.e. a model with fewer input features, will be much more robust to perturbations, faster and easier to understand, and much cheaper to maintain and update." Our own desire to follow the principle of parsimony motivated us to examine the DELFI-Pro data and determine how well LR models using only the measurements of CA125 and HE4 would perform. Such models, with similar architecture to that of the long-established ROMA, might give firmer insight into the added predictive power of DELFI-Pro's cfDNA-derived features. We present the results of this examination here.

Results

Collection of protein concentration data

Briefly, the blood samples from which Medina, *et al*. obtained their data were from two cohorts: a "discovery" cohort of samples from European studies, and a "validation" cohort of samples from American studies. Protein concentration levels for CA125 and HE4 were quantified using immunoassay measurements from these blood samples, in most cases from plasma, although a minority of measurements were made from serum samples.

In both discovery and validation cohorts, samples were collected from three classes of donors: those with no known ovarian lesions (labeled "healthy" hereafter), those with benign adnexal masses, and those with ovarian cancer. Both cohorts have two overlapping datasets: a "screening dataset" consisting of the healthy samples and the cancer samples; and a "diagnostic dataset" consisting of the samples from benign masses and the cancer samples.

The two datasets allow building of classification models in both a screening and a diagnostic context, and evaluation of the predictive power of an approach in both contexts.

To facilitate comparison between the models we built and the DELFI-Pro models, we maintained this same division of cohorts and use of classification contexts.

Building a protein-only logistic regression model

We chose to use a logistic regression model architecture for our machine learning approach. Other models are of course possible, but bearing in mind that our input data was only two-dimensional, that ROMA had achieved good performance with such an LR model, and that DELFI-Pro also utilized LR, we felt LR was the appropriate choice here. Our implementation of LR used a regularization penalty to reduce the amount and likelihood of overfitting, much like DELFI-Pro's implementation. To set parameters for our LR model, and determine appropriate data preprocessing steps, we focused our initial analysis on the discovery cohort.

A common and important early step in machine learning with laboratory analytes is to use the zlog transformation [13], which compensates for the fact that the range of values from pathological samples can be an order of magnitude higher than that seen in healthy samples. The zlog transformation both takes the logarithm of the input value so that the range of data is reduced, but also standardizes the result so that healthy data tends to be close to a value of zero. We applied this transformation first to the CA125 and HE4 values, and worked with the zlog values in place of the original protein concentrations moving forward. In this zlog feature space, we can see CA125 appears to distinguish between healthy and cancer samples well, but that HE4 may be needed to appropriately distinguish between benign masses and cancer samples (Fig. 1). The two zlog values are not strongly correlated, with a Pearson's R of 0.57 in the discovery cohort.

Similarly to Medina, *et al*., we evaluated each model's performance against the appropriate discovery data in a 5-fold stratified cross validation which we repeated 10 times, and we recorded the mean score of a sample across all 10 repeats of cross validation. To evaluate the performance of the model, we use the receiver operating characteristic (ROC) area under the curve (AUC). After cross validation, our screening protein-only model had an AUC of 0.96, equal to the 0.96 reported by DELFI-Pro (Fig. 2). In the diagnostic context, our protein-only model had an AUC of 0.86, slightly less than the cross validation AUC of 0.88 reported by DELFI-Pro (Fig. 3).

In addition to this cross validation work, we also fit the same models to the full discovery datasets, so that the models could be examined and run on the validation cohorts. Examining the coefficients of the LR models, we see that CA125 does indeed provide more influence than HE4 in a screening context: CA125 has a coefficient of 1.25, compared to HE4's 1.02. In a diagnostic context, the opposite is true: CA125's coefficient is 0.14, while HE4's is 1.15, indicating greater influence from HE4's concentration. This can also be seen in Fig. 4, where the

decision boundary in the discovery dataset is more horizontal in the diagnostic context (indicating that HE4 influences the model more) than it is in the screening context.

Validation and performance of the fitted models

While cross validation results are useful, testing on a separate and unrelated dataset is considered to be a more reliable test of a model's generalizability [14]. As did Medina, et al., we ran the models fit to the discovery cohorts on the corresponding validation cohorts. While our protein-only models performed very similarly to DELFI-Pro in cross validation, our models substantially outperformed DELFI-Pro on the validation cohorts. Our screening model achieved an AUC of 0.99, above the corresponding DELFI-Pro AUC of 0.93 (Fig. 2); and our diagnostic model achieved an AUC of 0.86, also above the DELFI-Pro diagnostic validation AUC of 0.81 (Fig. 3). We also compared our screening model against results from an unpublished protein-only model created by the DELFI-Pro authors (found in the online code repository associated with the DELFI-Pro publication), where our validation AUC of 0.99 was slightly higher than the unpublished DELFI model's AUC of 0.98 (Fig. S1).

Discussion

The results from Medina, *et al*. are largely consistent with our results here. The concentrations of CA125 and HE4 are valuable biomarkers by themselves, but combining them using a machine learning model provides even greater predictive power. We go further than the DELFI-Pro authors here, however, in examining and reporting the performance of the two proteins without any cfDNA-associated features. When evaluating a complex model such as DELFI-Pro, this two-protein model would seem to be an appropriate baseline to compare to, and perhaps more appropriate than the comparisons to the two protein concentrations in isolation that we find in the original publication.

When compared to the DELFI-Pro models' performance on the validation cohorts, we see superior performance from our simpler models. We also see concordant performance with a protein-only model available in the DELFI-Pro code repository, giving us further confidence in the results of our parsimonious approach. Given these validation results and the very similar cross validation performance between our models and DELFI-Pro on the discovery cohorts, it appears that the simpler models exhibit improved generalizability compared to the DELFI-Pro models. Our protein-only models would also tend to be easier, faster, and cheaper to perform than the DELFI-Pro approach. This is because a laboratory test using our models would only require the quantification of protein concentrations, rather than also needing to prepare, sequence, and bioinformatically analyze DNA libraries. In light of these results, the additional predictive utility over CA125 and HE4 that would be provided by DELFI-Pro's cfDNA-derived features remains unclear.

Our results suggest that the ROMA approach can be successfully adapted to screening. Even without the precedent of ROMA, the combination of CA125 and HE4 makes sense to improve

detection accuracy of ovarian cancer, especially in light of the clear orthogonality of the two proteins' concentrations as seen in Fig. 1. Adding more orthogonal biomarkers to an LR model is quite reasonable, as long as the addition of the new biomarkers is shown to provide increased predictive value. As new biomarkers for ovarian cancer are investigated and shown to be orthogonal to both CA125 and HE4, it would certainly be reasonable to examine them in a combined model (be it LR or another machine learning architecture) with CA125 and HE4. It will remain important to compare such a potential improvement against a suitable baseline model, however, and the evidence we presented here strongly supports using a baseline model that combines these two proteins rather than using each protein in isolation. The comparison against such a baseline model will help to ensure that each new feature actually provides a meaningful advance, and that the complexity added by new features is merited by improvement in accuracy.

Methods

Data collection

We collected all data used here from the "delfipro2024" GitHub repository [15], which the DELFI-Pro authors made public as supporting material along with the DELFI-Pro publication. We also obtained in that repository scores from the protein-only screening model generated by the DELFI-Pro authors, along with the script ("code/proteins_screening_model.r") to generate that model.

Data preprocessing

As defined by Al-Mekhlafi, et al. [13], the zlog transformation requires the use of a reference range derived from a healthy population, rather than calculating the mean and standard deviation (SD) from our own data. This use of a reference range is done to mitigate against outliers that could influence the mean and SD, and is based upon the 2.5th and 97.5th percentile values of a healthy population.

To perform the zlog transformation, we could not easily find firm population-wide distributions for CA125 or HE4, and so we adopted values of 35 U/mL as the upper reference limit for CA125, and 140 pmol/L as the upper reference limit for HE4, based on the highest limits given by Dochez, et al. [2]. For the lower reference limits, we used the recommendation given by Haeckel, et al. [16] to set the lower reference limit to 15% of the upper limit (i.e., 5.25 for CA125, and 21 for HE4), because we could not find firm guidance on a lower reference limit for either protein. These reference limits, then, served as our estimates for the 2.5th and 97.5th percentile values for the two proteins.

Logistic regression model training

When building our regression models, we used default values for all parameters except for one. The one exception was the class_weight='balanced' argument, which ensured that even though

there were approximately twice as many noncancer samples as cancer samples in the discovery cohort (for either of the screening or diagnostic contexts), the class imbalance would be accounted for in the model's fitting. This use of default values means our regularization penalty was an L2 (ridge regression) penalty term that was weighed equally with the error term of the objective function [17].

Software analyses

We used the scikit-learn package (v0.23.2) to build our logistic regression models, matplotlib (v3.5.1) and seaborn (v0.11.2) to create plots, and pandas (v1.3.5) and numpy (v1.21.5) for operating on tabular data and doing general arithmetic. All code was written in Python (v3.10.12) using a Jupyter (v6.4.8) notebook.

Data availability

Our Jupyter notebook containing all code we wrote for this project, along with copies of the data we used, are archived with and freely available from Zenodo [18].

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Figures

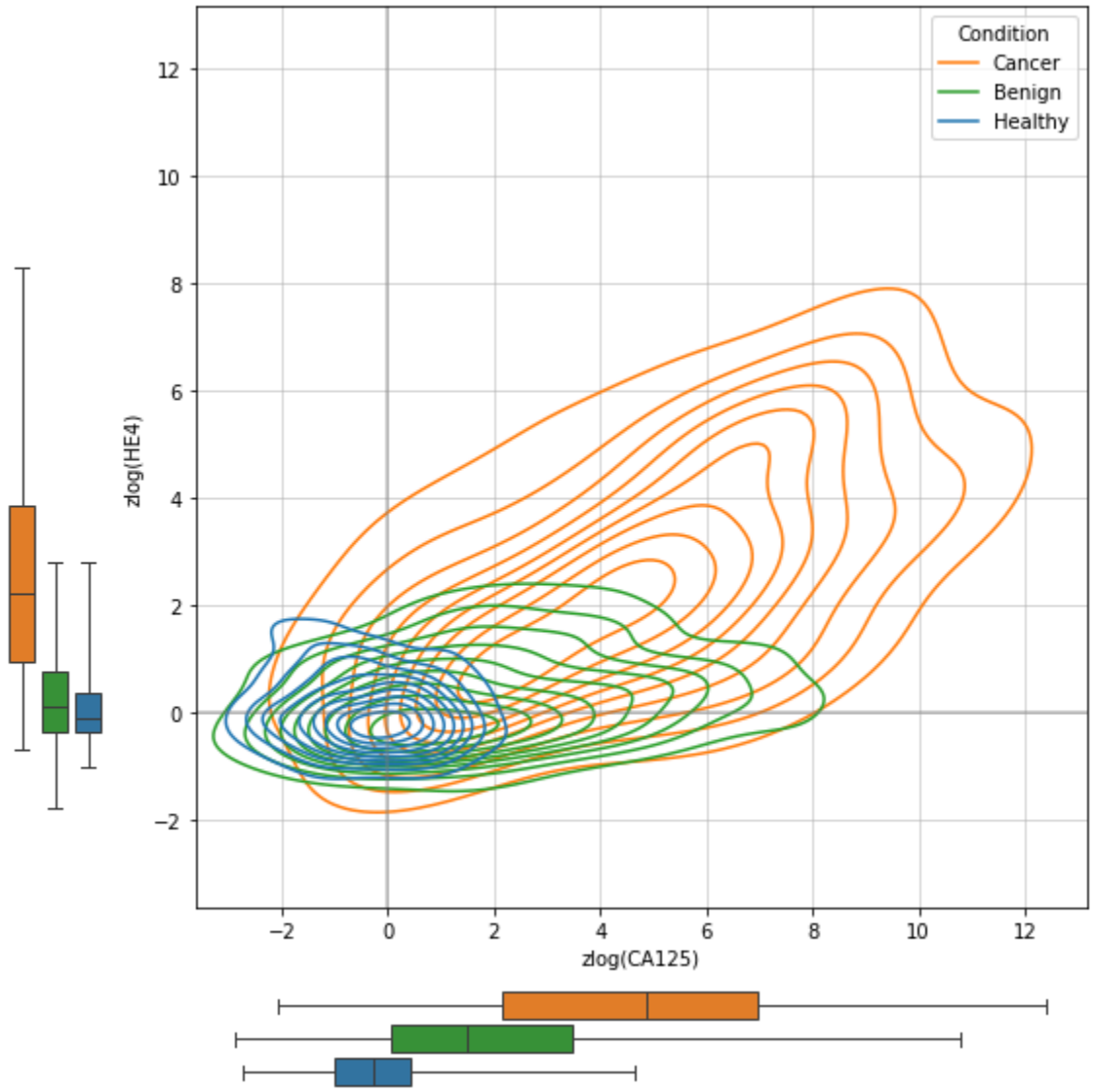

Figure 1. Kernel density estimation plot of zlog-transformed protein concentration values in the discovery cohort. Marginal distributions of the two protein levels within the three conditions of interest are shown to the left and under the corresponding axes, with boxplots indicating the interquartile range and whiskers representing the range from the minimum to maximum values.

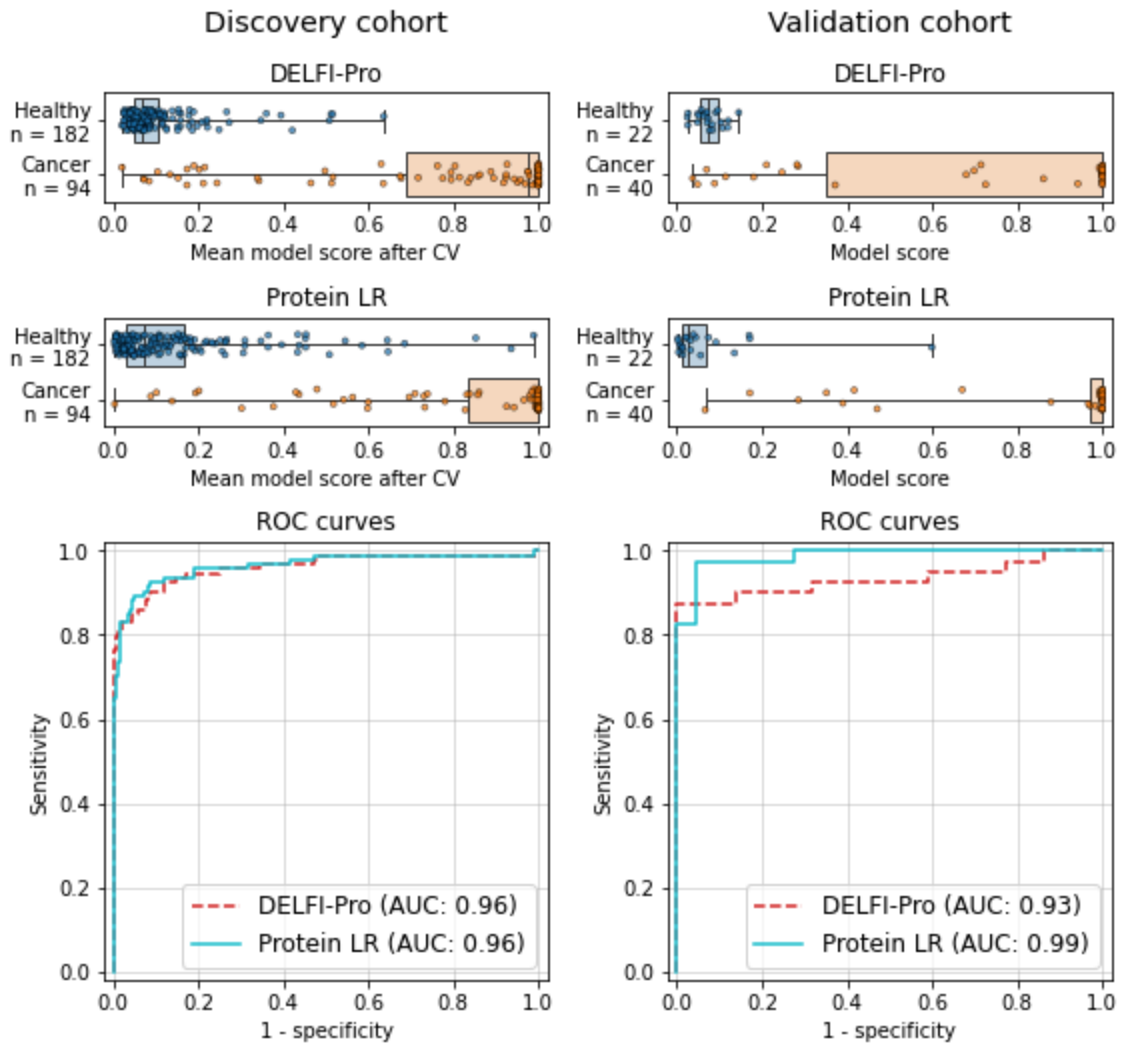

Figure 2. Logistic regression model performance in a screening context. Cross validation ("CV") results for the discovery cohort, and validation results on the validation cohort are shown for both the DELFI-Pro screening model and a two-protein logistic regression ("Protein LR") screening model. Both models seek to distinguish between samples from healthy donors and samples from patients with ovarian cancer. Receiver operating characteristic (ROC) curves demonstrate the performance of the two models at various score thresholds, with the area under the curve (AUC) growing proportionally to model accuracy.

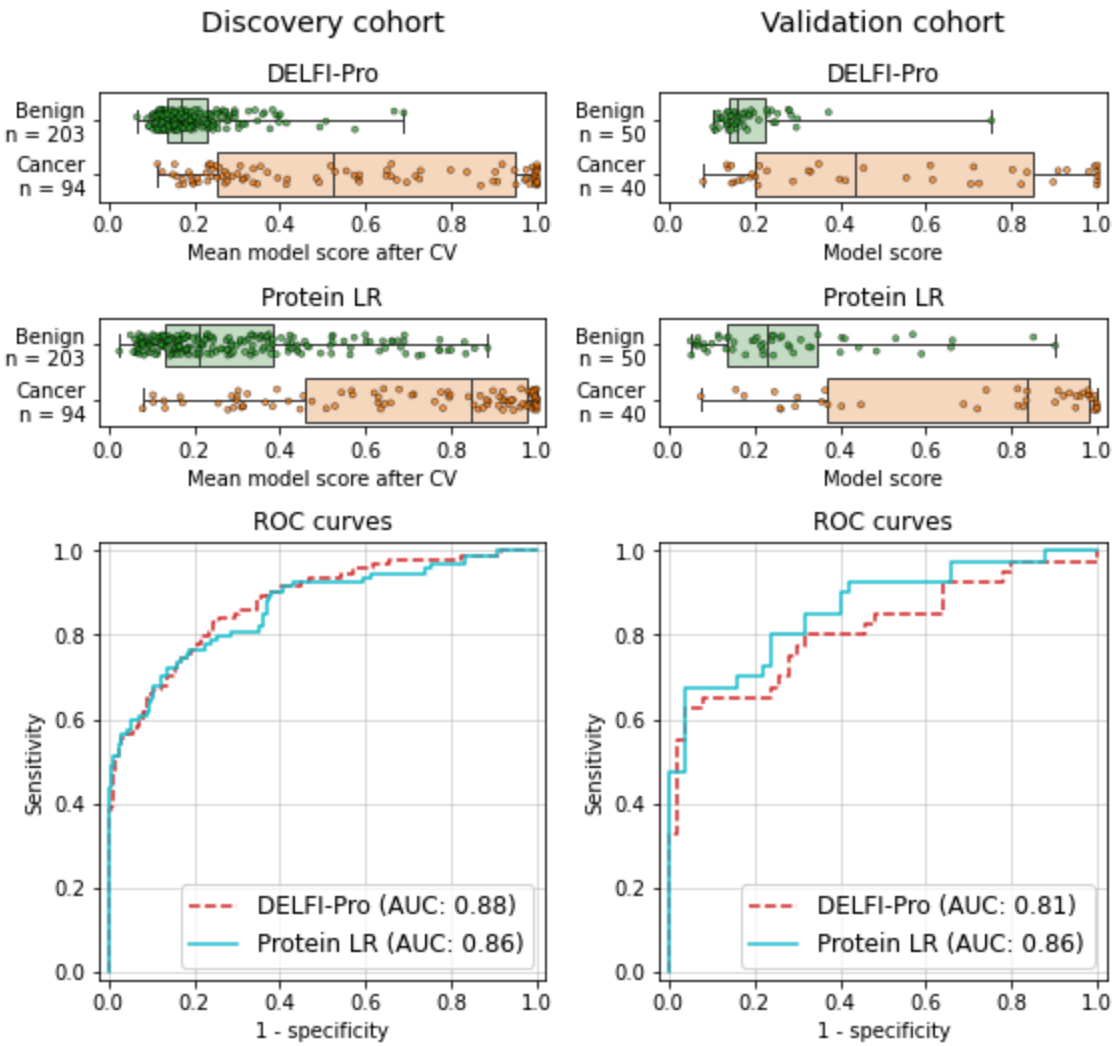

Figure 3. Logistic regression model performance in a diagnostic context. Cross validation ("CV") results for the discovery cohort, and validation results on the validation cohort are shown for both the DELFI-Pro diagnostic model and a two-protein logistic regression ("Protein LR") diagnostic model. Both models seek to distinguish between samples from donors with benign adnexal masses and samples from patients with ovarian cancer. Receiver operating characteristic (ROC) curves demonstrate the performance of the two models at various score thresholds, with the area under the curve (AUC) growing proportionally to model accuracy.

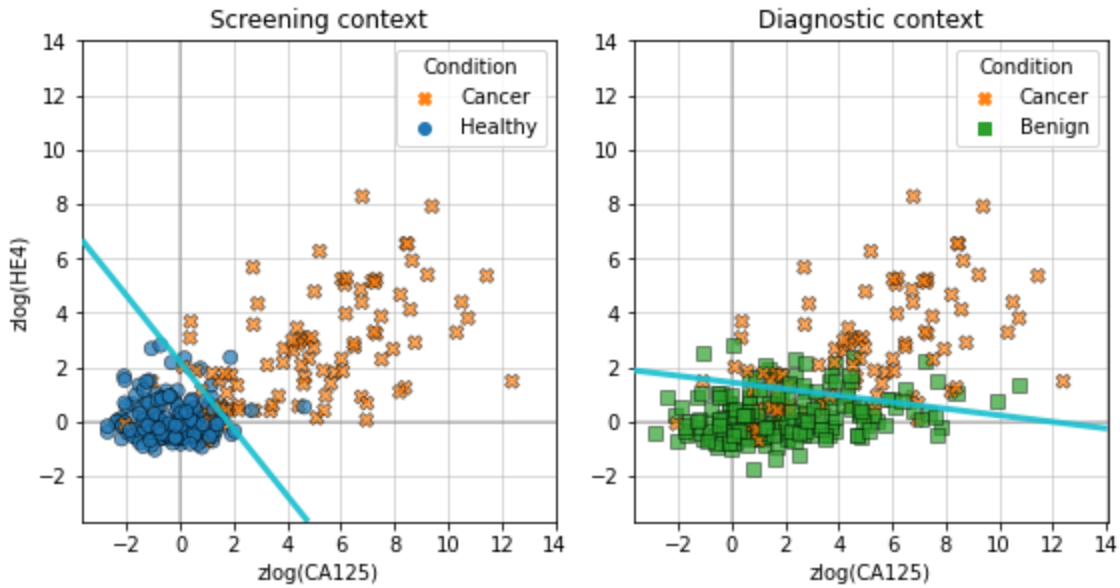

Figure 4. Decision boundaries learned by logistic regression models on the discovery cohort. On the discovery cohort, two protein-only models were fit to the data. In the screening context, the model distinguishes between samples from healthy donors and samples from patients with ovarian cancer. In the diagnostic context, the model distinguishes between samples from donors with benign adnexal masses and samples from patients with ovarian cancer. The decision boundaries for the two models are drawn in cyan.

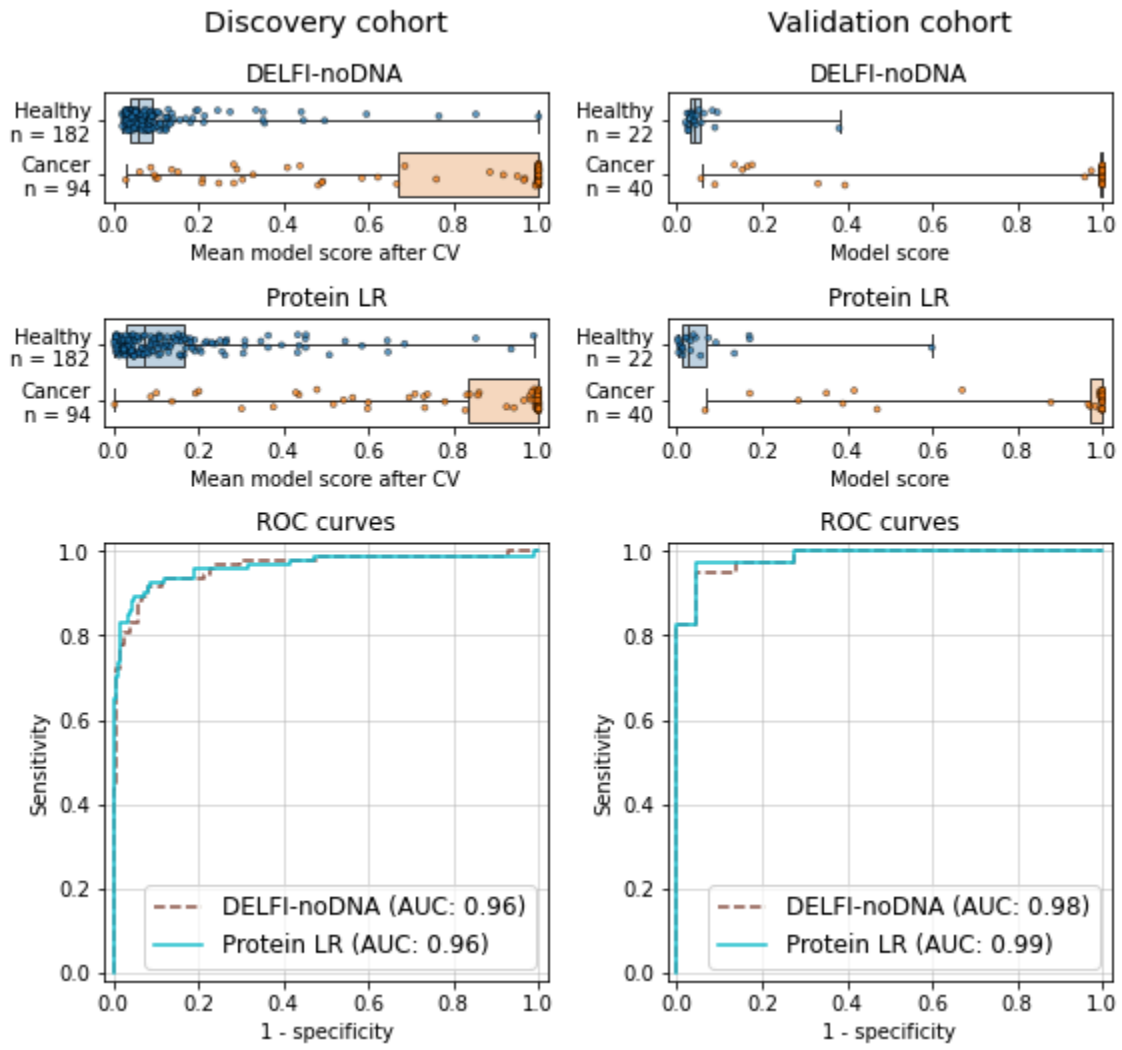

Figure S1. Comparison of our protein screening model with a model made available by DELFI-Pro authors. Cross validation ("CV") results for the discovery cohort, and validation results on the validation cohort are shown for both the DELFI-Pro authors' two-protein logistic regression screening model ("DELFI-noDNA") and our two-protein logistic regression ("Protein LR") screening model. Both models seek to distinguish between samples from healthy donors and samples from patients with ovarian cancer. Receiver operating characteristic (ROC) curves demonstrate the performance of the two models at various score thresholds, with the area under the curve (AUC) growing proportionally to model accuracy.