



dev>scope

Helicobacter Pylori (HP)

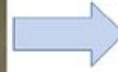
- Bacteria that infects the stomach
- This pathogen colonizes approximately 50% of the world's population [1]
- Infection with HP causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with *H. pylori* is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide [1]



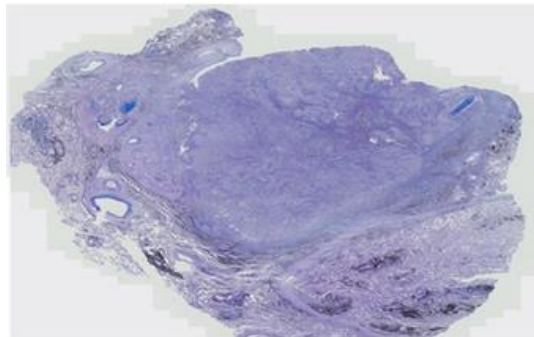
[1] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952980/#:~:text=pylori%20causes%20chronic%20inflammation%20and,of%20cancer%2Drelated%20deaths%20worldwide.>



(a)



(b)



(c)



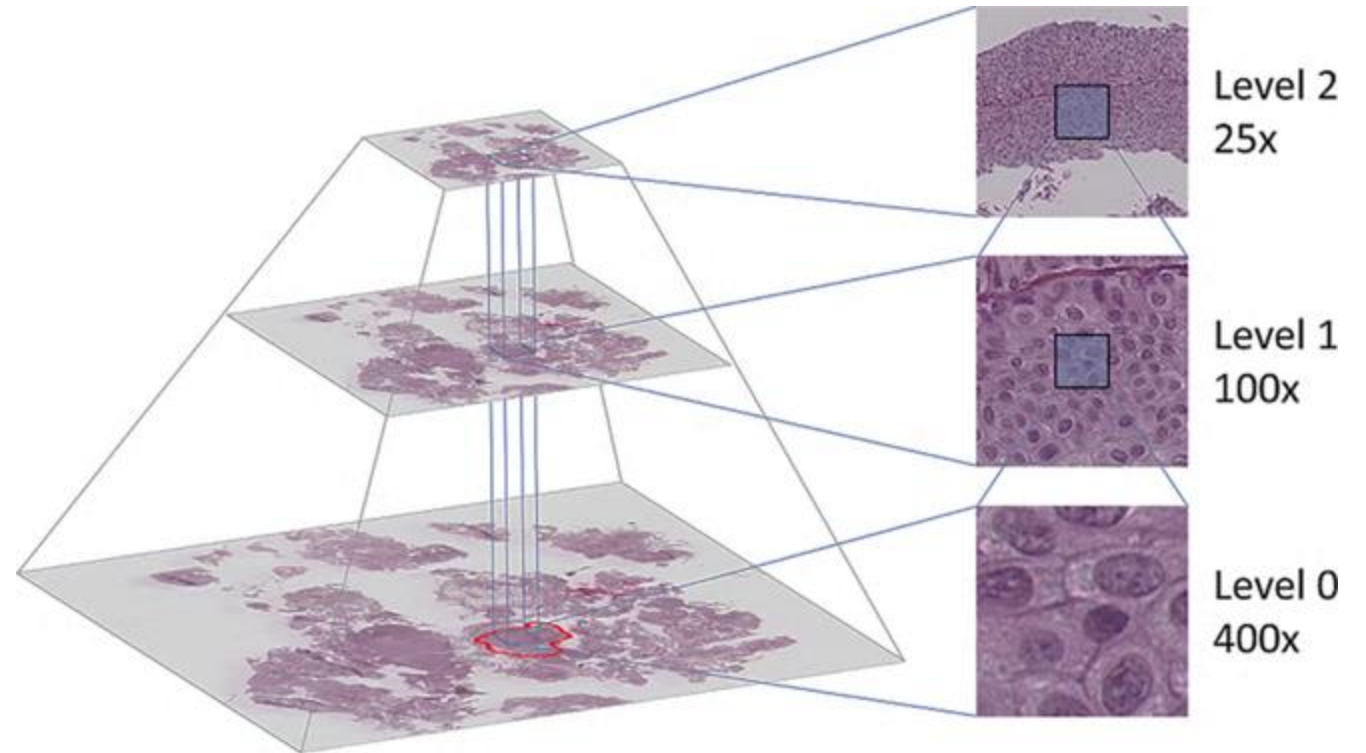
(d)

- One of existing methods used to diagnose infection by HP is Histology.
- This method consists in collecting a biopsy from the patient and analyzing the resulting slide.
- Using a microscope (or **digital pathology**) it is possible to see the cells and, in this case, the bacteria.

[2] <https://www.researchgate.net/publication/358240628>

Whole Slide Images (WSI)

- Very large images that represent a scanned slide.
- **Pyramidal structure:** one image contains many levels, which representing a “version” of the slide with a specific resolution.



[3] <https://journals.sagepub.com/doi/10.1177/1533033820946787?icid=int.sj-abstract.similar-articles.1>

HP in a WSI

Slide classification: 0, 1+, 2+ or 3+

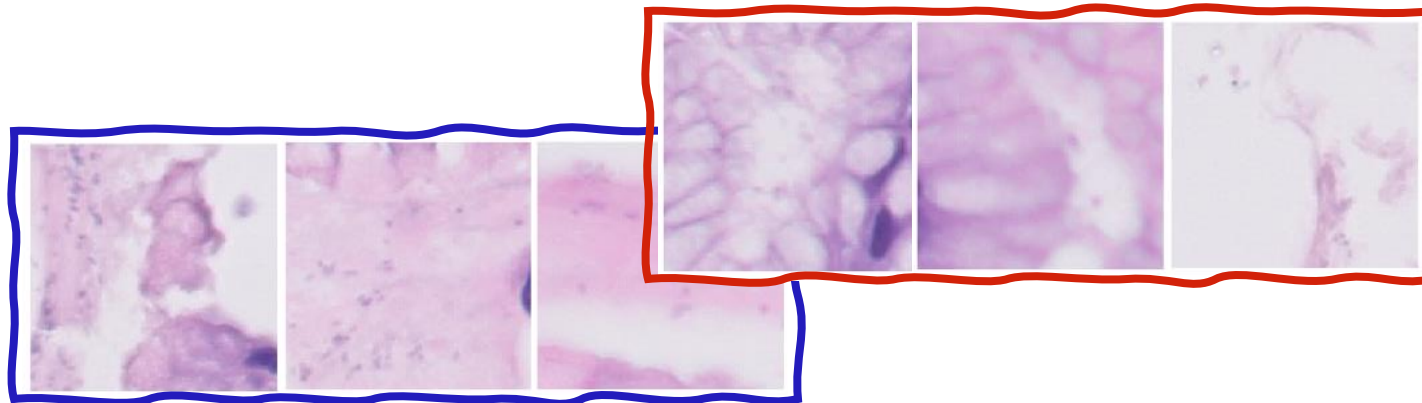
Depends on the quantity of bacteria present in the slide:

normal, no bacteria (0)

mild, focal few bacteria (1)

moderate, more bacteria in several areas (2)

marked, abundance of bacteria in most glands (3)



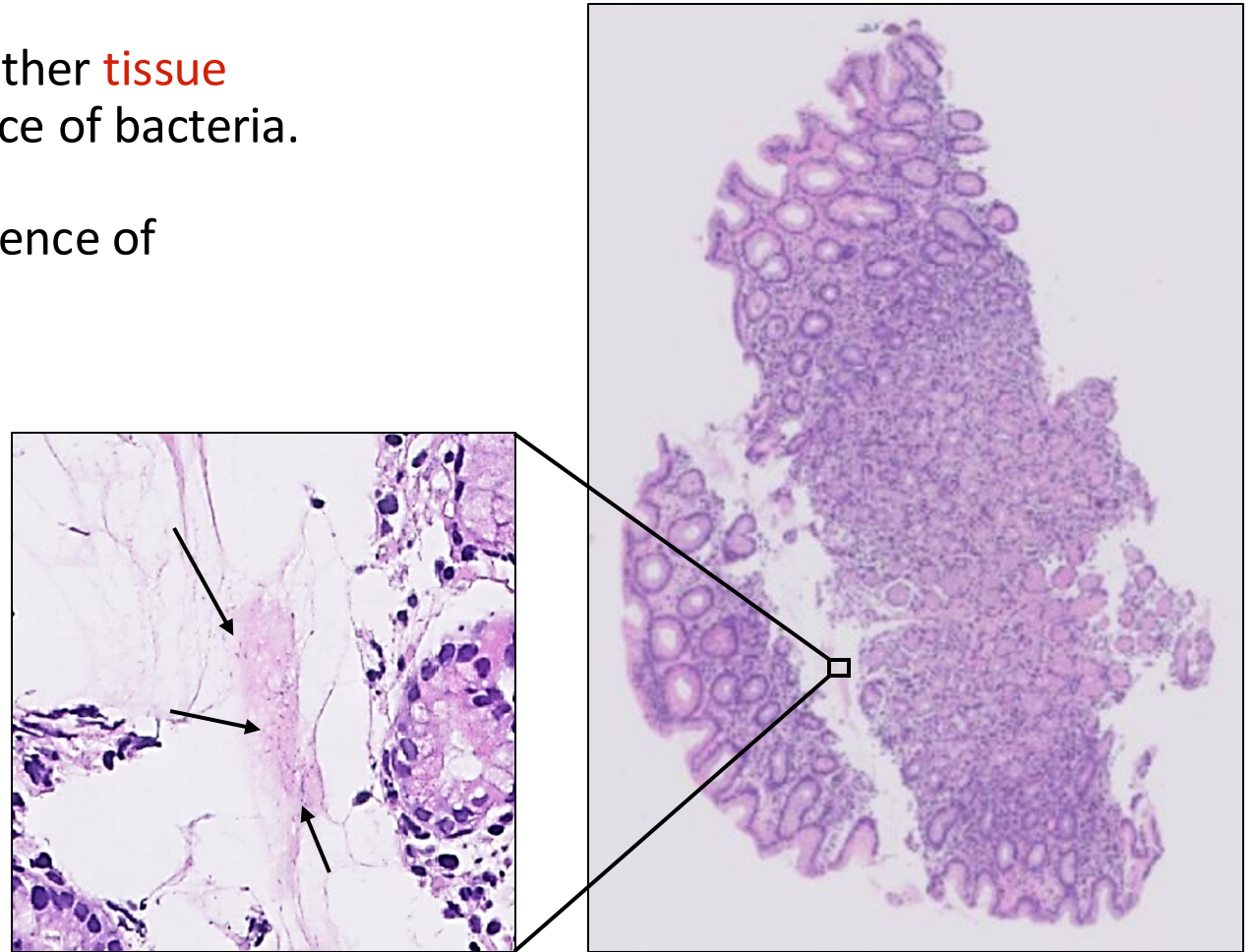
Our objective is to use H&E for bacteria detection and slide classification



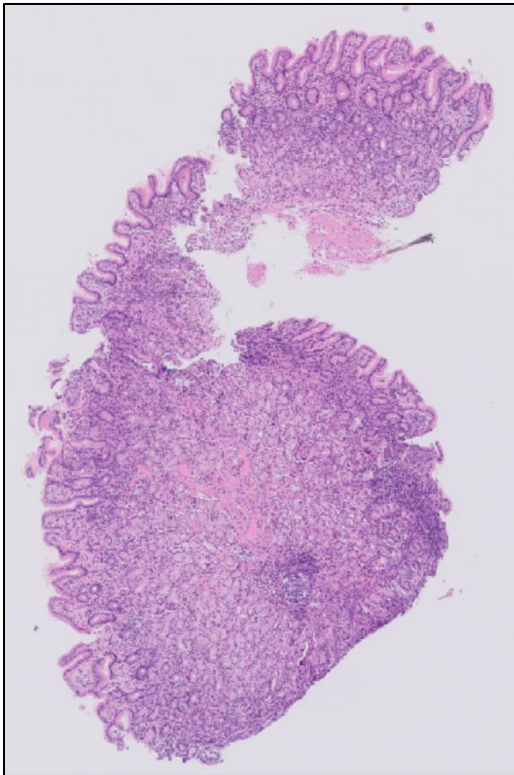
[4] https://journals.lww.com/ajsp/abstract/1996/10000/classification_and_grading_of_gastritis_the.1.aspx

Pathologists usually look for **context** and other **tissue characteristics** that might indicate the presence of bacteria.

One of these characteristics is the presence of inflammation.



Inflammation

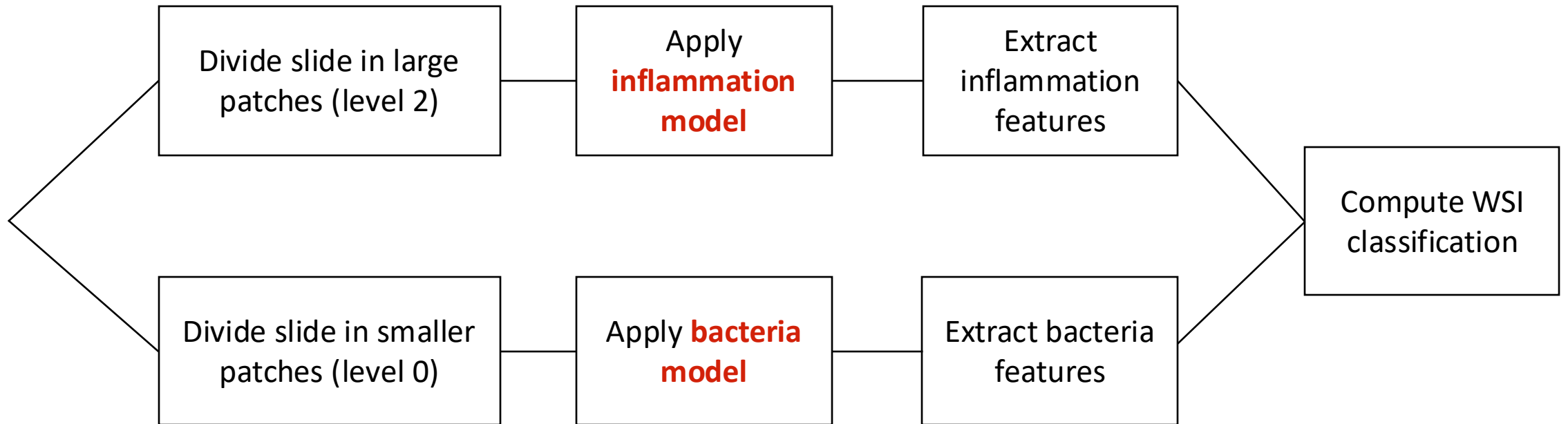


- Pathologists usually look for external signs of bacteria infection, that are easier to detect in the slide at a lower magnification, such as inflammation
- The presence of inflammation in a slide is correlated with HP infection.

“In this study, more than 90% of people infected with H. pylori experienced varying degrees of gastritis, with moderate gastritis (51.10%) having the highest incidence.” [4]

[5] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5727686/>

Approach: Using bacteria and inflammation features to obtain the global WSI classification

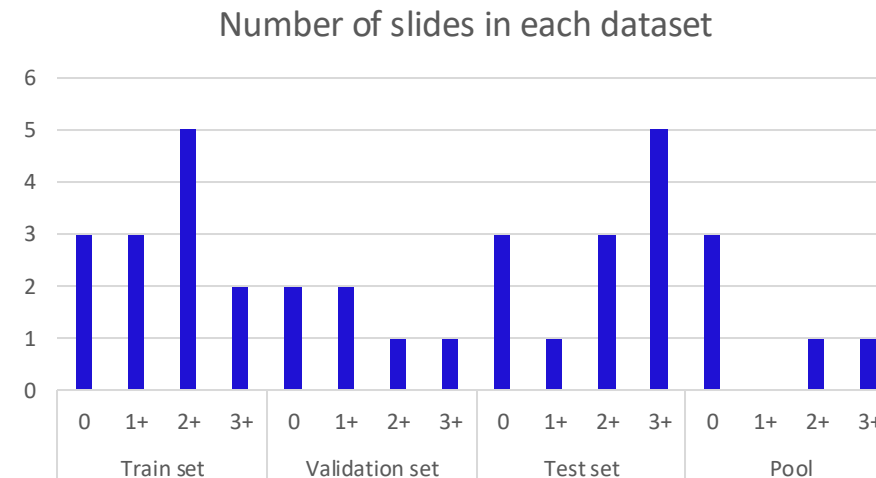
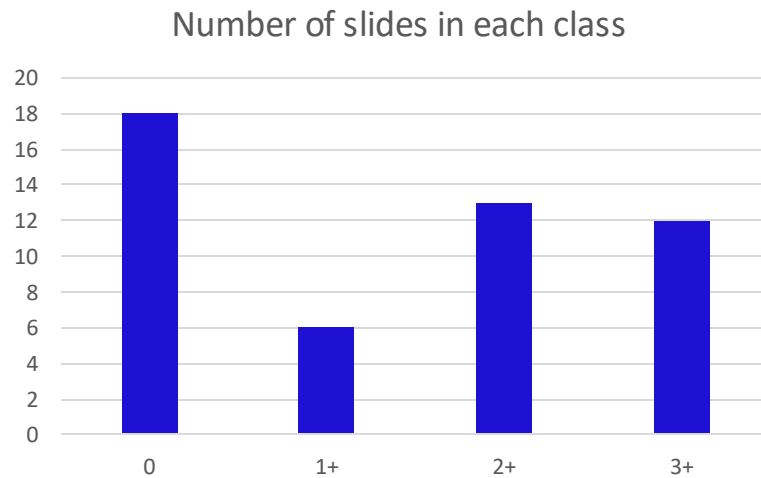


Dataset



Dataset

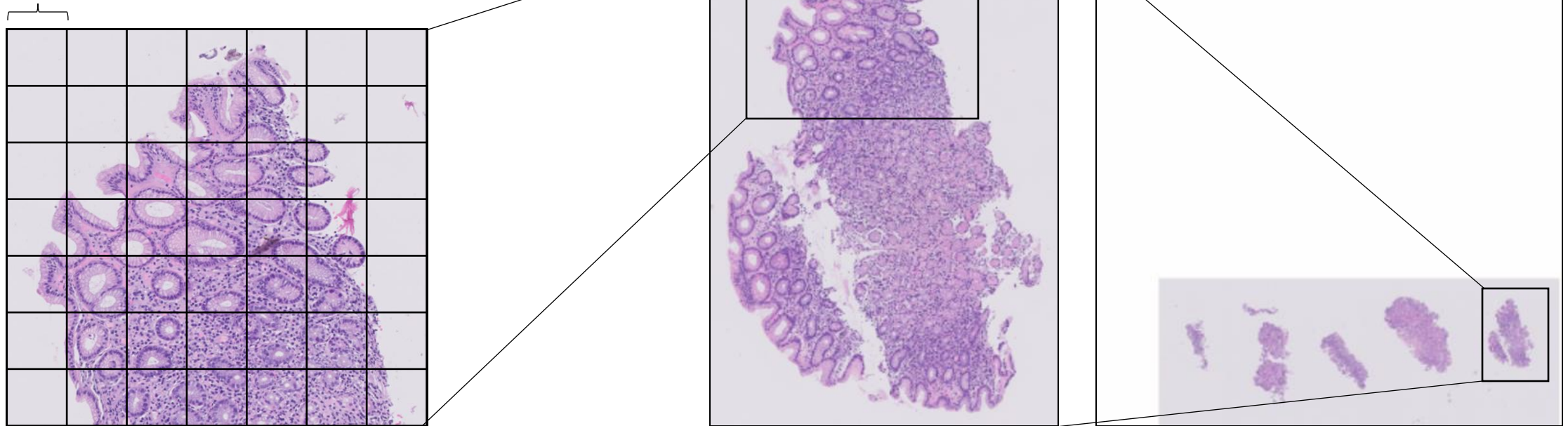
- 41 patients and a total of 49 slides;
- 25 of the patients were split in train, validation and test, according to the frequency of slide and patch label. The remaining patients form the pool dataset;
- No annotations for bacteria or inflammation location, all we have is the slide global (WSI) classification.



Dealing with WSI - Patches

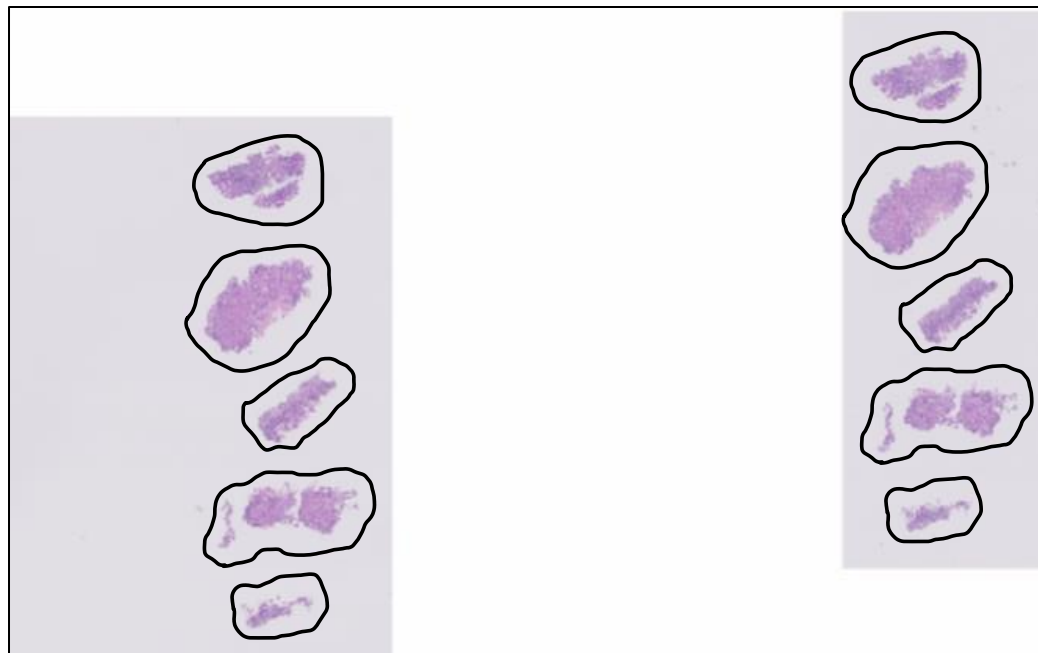
- Using image patches and considering it a classification problem at this level.

patch



Dealing with WSI - Patches

- Not all patches in a WSI are relevant. Most of them are blank (background), and don't contain any tissue. To exclude the blank patches, a threshold was applied;
- Then, the **coordinates of central pixel for each tissue patch** was saved.

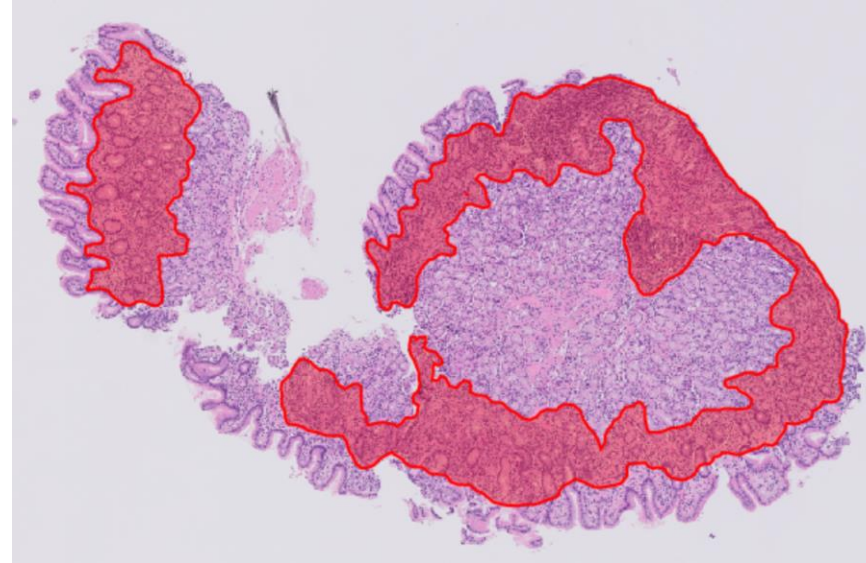
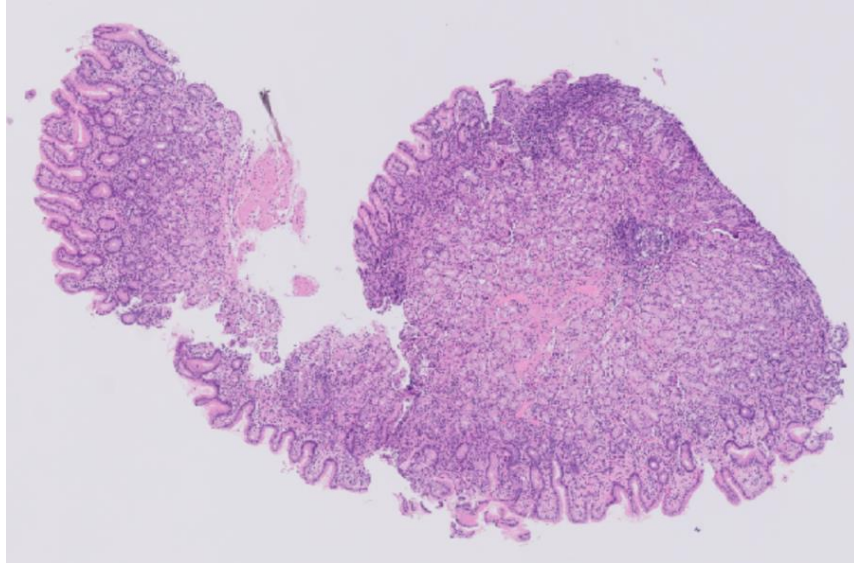


Inflammation Detection



Inflammation Annotations

- Manual annotation of inflammation areas using QuPath, for the train, validation and test dataset slides;
- To detect inflammation, larger patches should be used – including more context. Thus, 256 x 256 pixels patches (on level 2) were generated;
- Patches are considered positive if they are within inflammation mask areas.



Inflammation Annotations

- Datasets size:

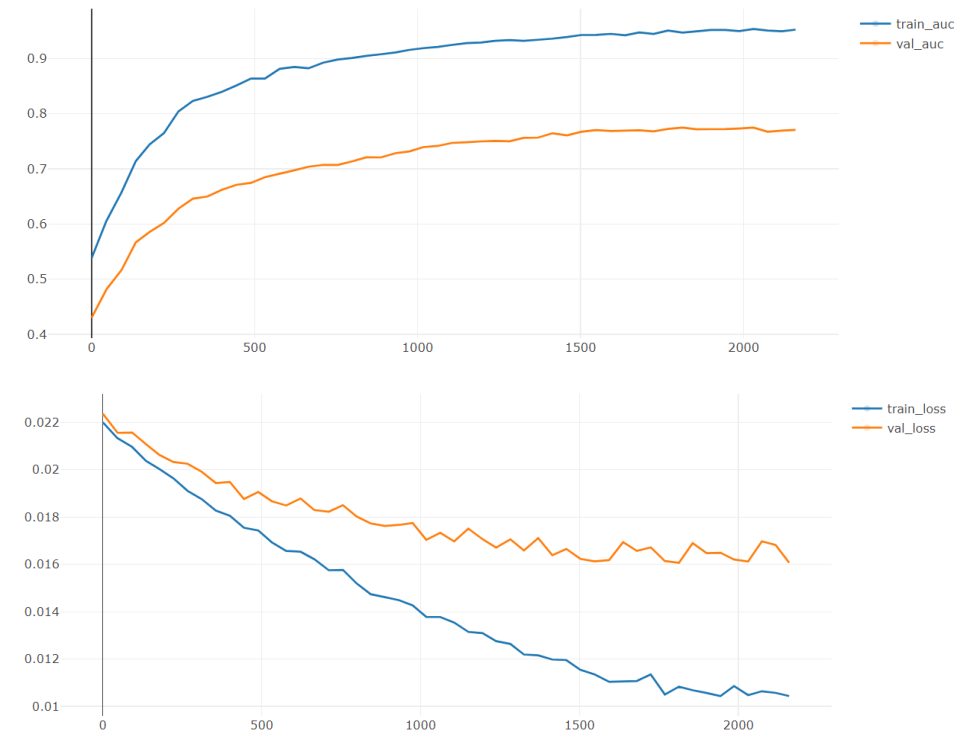
Train: 674 positive samples, 1024 negative samples

Val: 90 positive samples, 227 negative samples

Test: 292 positive samples, 416 negative samples

- DenseNet121

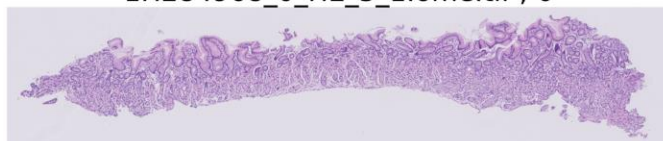
- Using data augmentation techniques



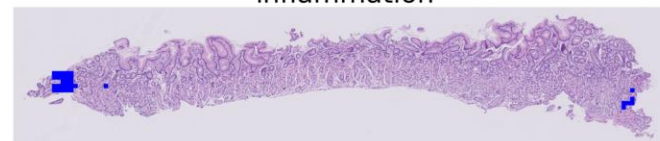
AUC	Opt. Thresh	Precision	Recall	Accuracy	F1 Score
0.7727	0.4588	0.6854	0.6267	0.7274	0.6547

Inflammation Detection Results

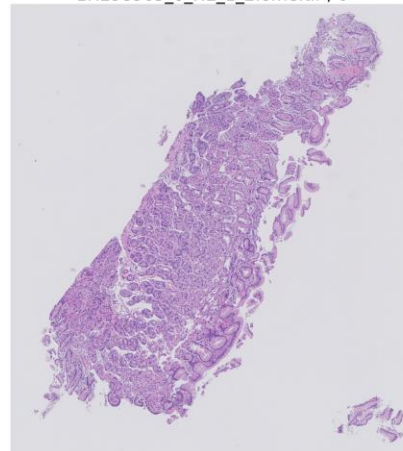
1H284968_0_HE_3_1.ome.tif ; 0



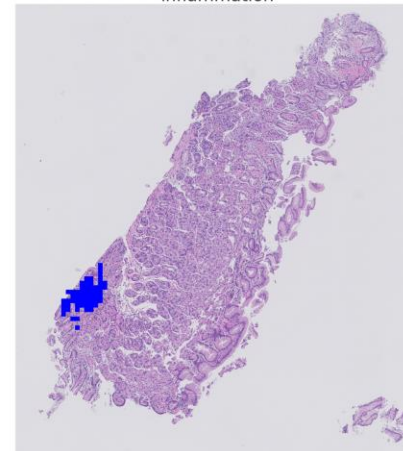
inflammation



1H298965_0_HE_1_2.ome.tif ; 0

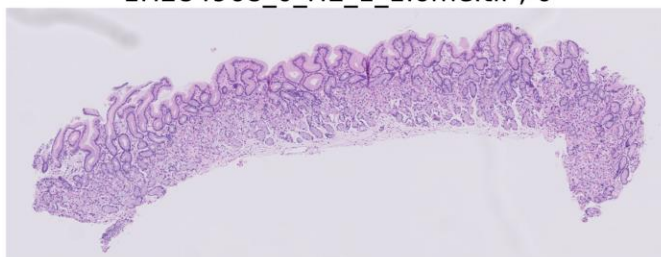


inflammation

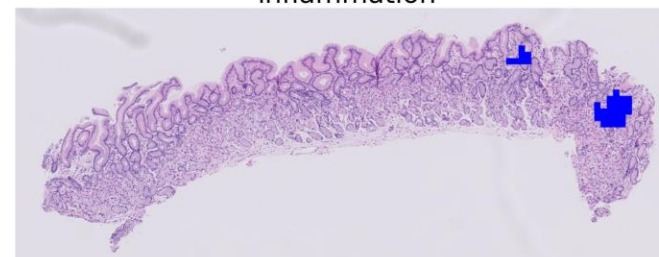


Negative (0) slides (for
bacteria)

1H284968_0_HE_1_1.ome.tif ; 0

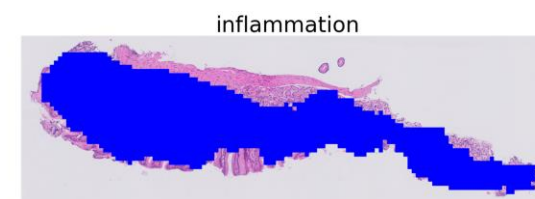
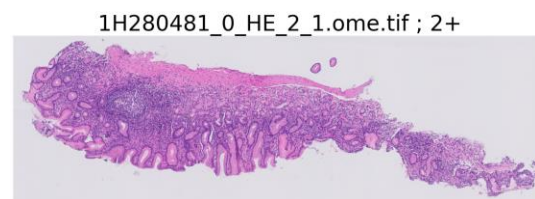
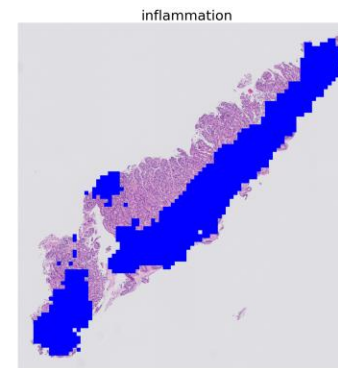
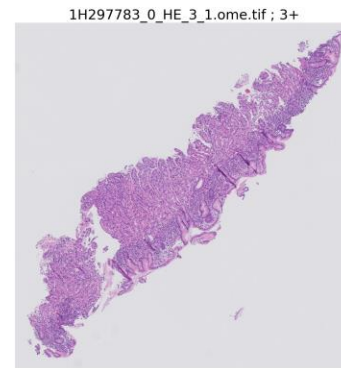
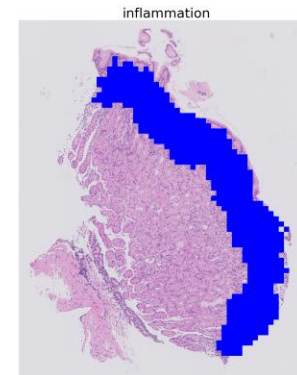
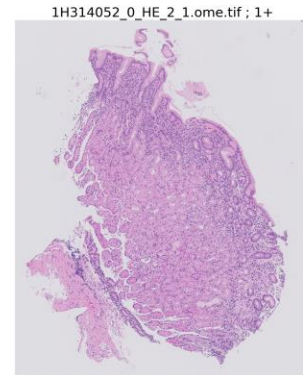


inflammation



Inflammation Detection Results

Positive (1+, 2+, 3+)
slides (for bacteria)



Inflammation Results

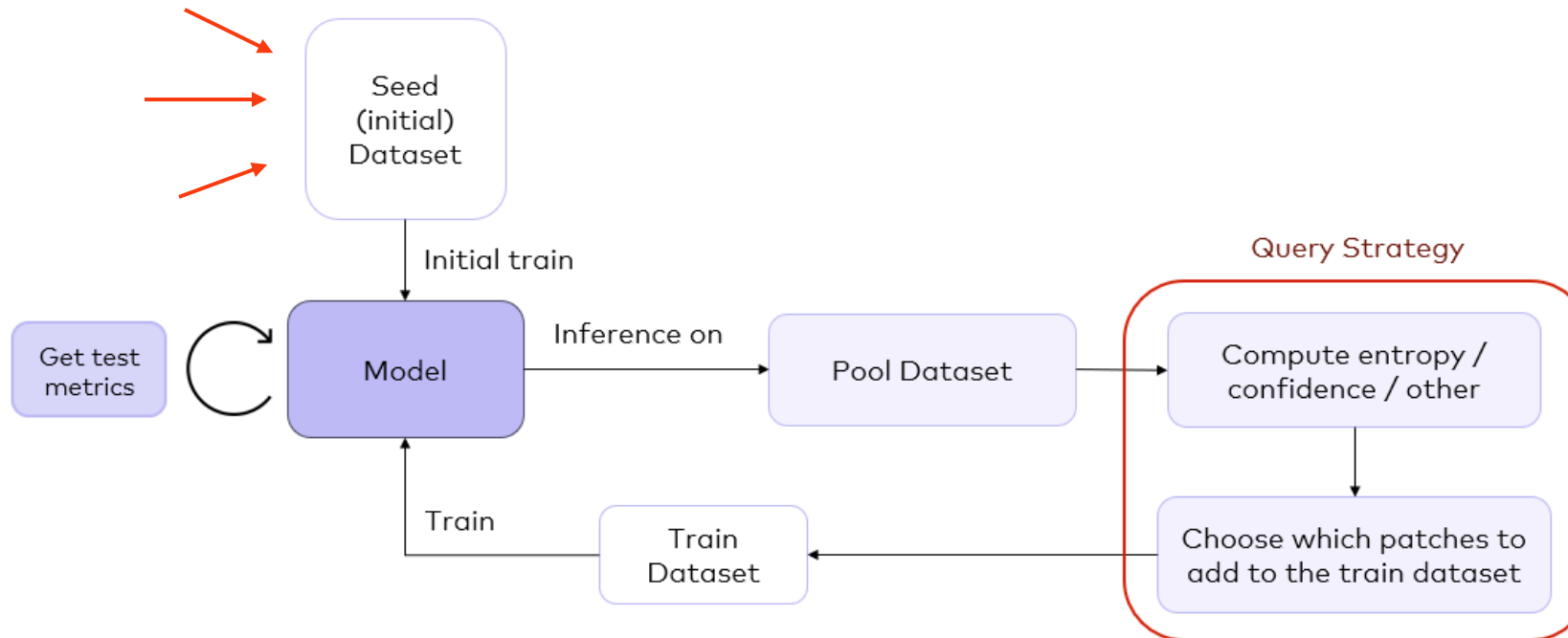
- HP causes inflammation in the tissue, however, inflammation can be seen without the presence of HP. Also, the intensity of inflammation is not a good indicator for the intensity of bacteria in the slide, and it is not site specific (inflammation is not necessarily near bacteria).
- Thus, the inflammation model can be used as a helper for a HP slide classification algorithm, but not on its own (for the identification and classification of bacteria).

Bacteria Detection



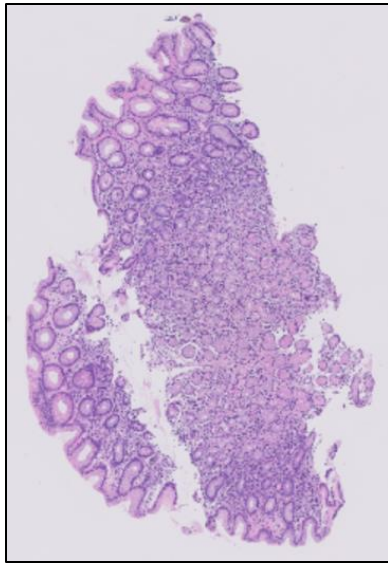
Approach – Active Learning

- In order to build a dataset, we need bacteria annotations;
- With the objective of building a representative dataset, active learning based strategies were adopted.



Initial Dataset Creation

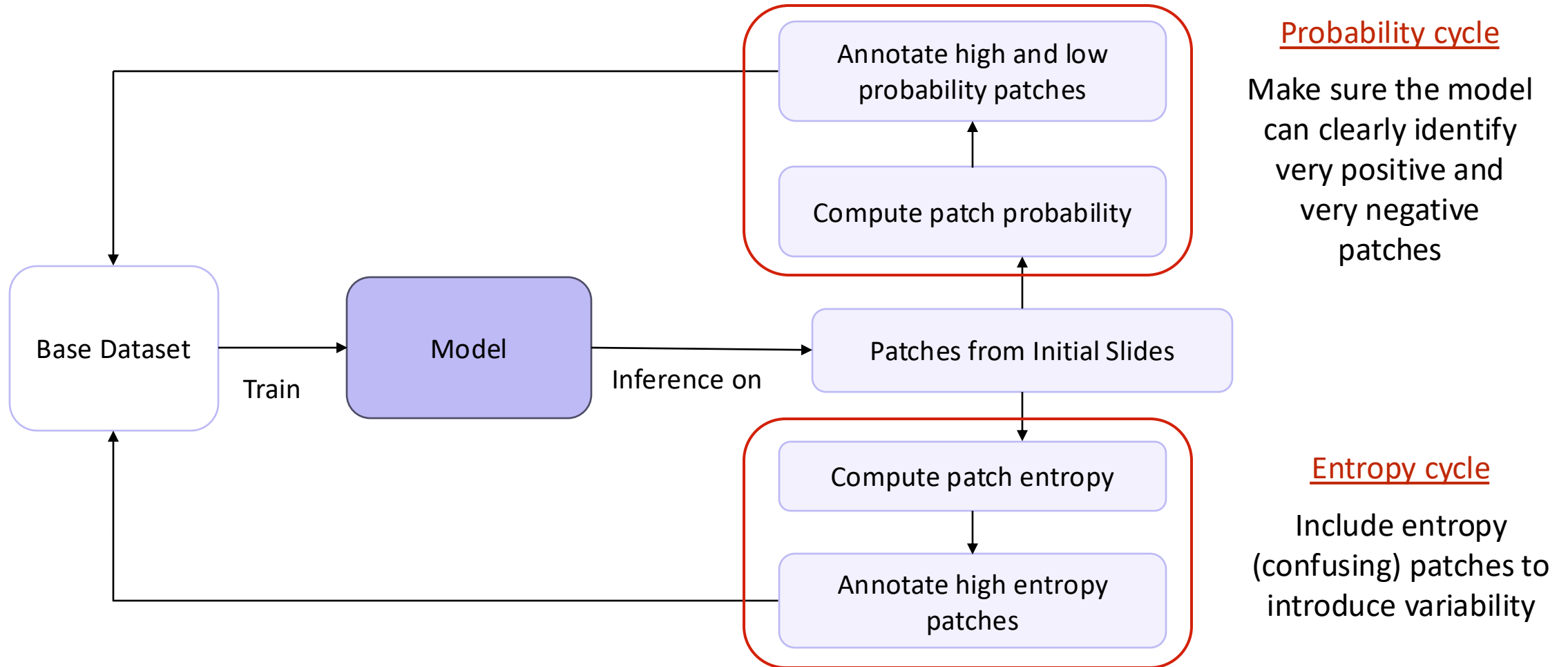
- Obtention of patches from the train, validation and test slides;
- In this case, we use smaller patches (128 x 128 pixels on level 0) – with this size, we can spot bacteria and some context;
- Very positive and very negative patches were selected to form an easy base dataset.



Train		Validation		Test	
Positive	Negative	Positive	Negative	Positive	Negative
178	220	43	61	164	174

This base dataset is small and needs to be expanded to form a good initial dataset.

Initial Dataset Creation



Entropy Cycle - Entropy for Imbalanced Dataset

- The query strategy is the method used to select new patches for annotation. These methods can be based on the confidence or entropy computed for each patch.
- In this problem, the positive/negative ratio is highly imbalanced. As there are a lot more negative images, there is a much higher probability that negative patches are selected for annotation, which might worsen the data imbalance problem.
- There is a need to adapt the query strategy, so it balances out the minority and majority class.

$$H_w(w_1, w_2, \dots, w_n; p_1, p_2, \dots, p_n) = - \sum_{k=1}^n w_k p_k \log p_k$$

Weight based on
class frequency

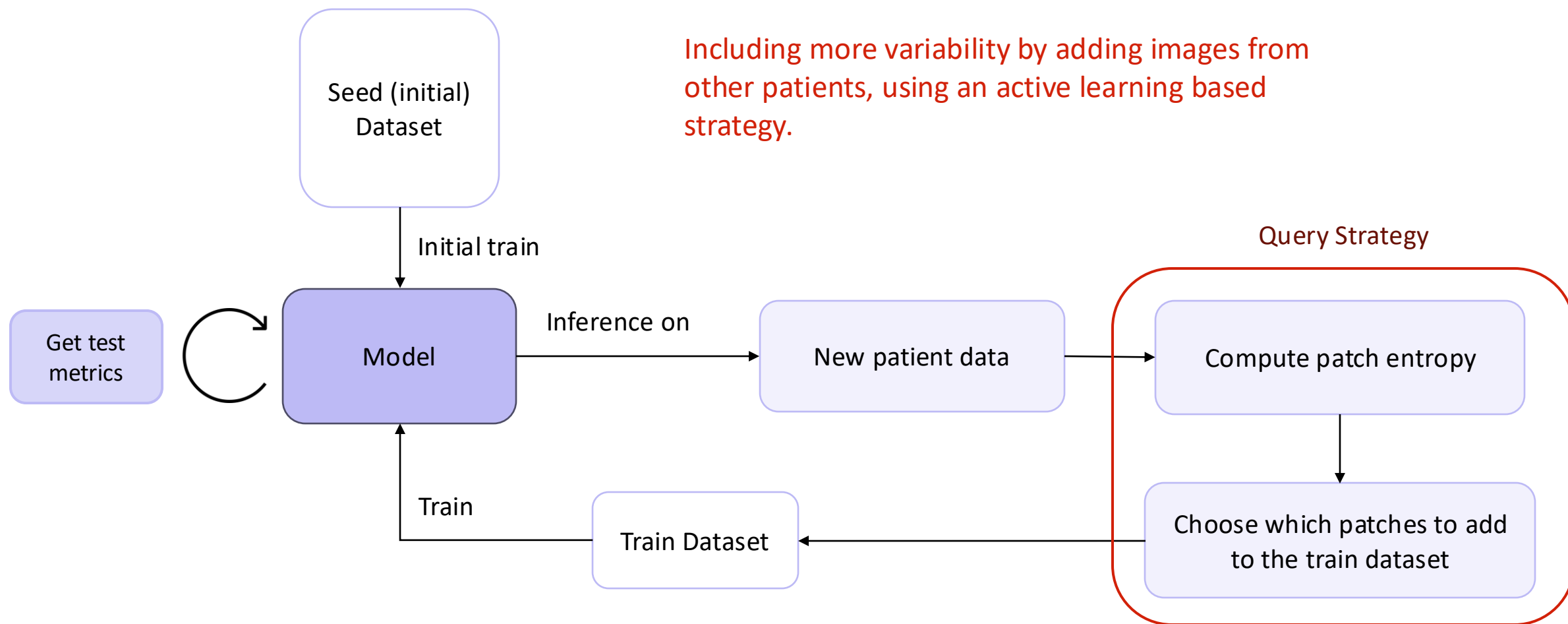
Initial Dataset Creation

- 2 probability cycles were done, followed by 4 entropy cycles, obtaining an expanded initial dataset

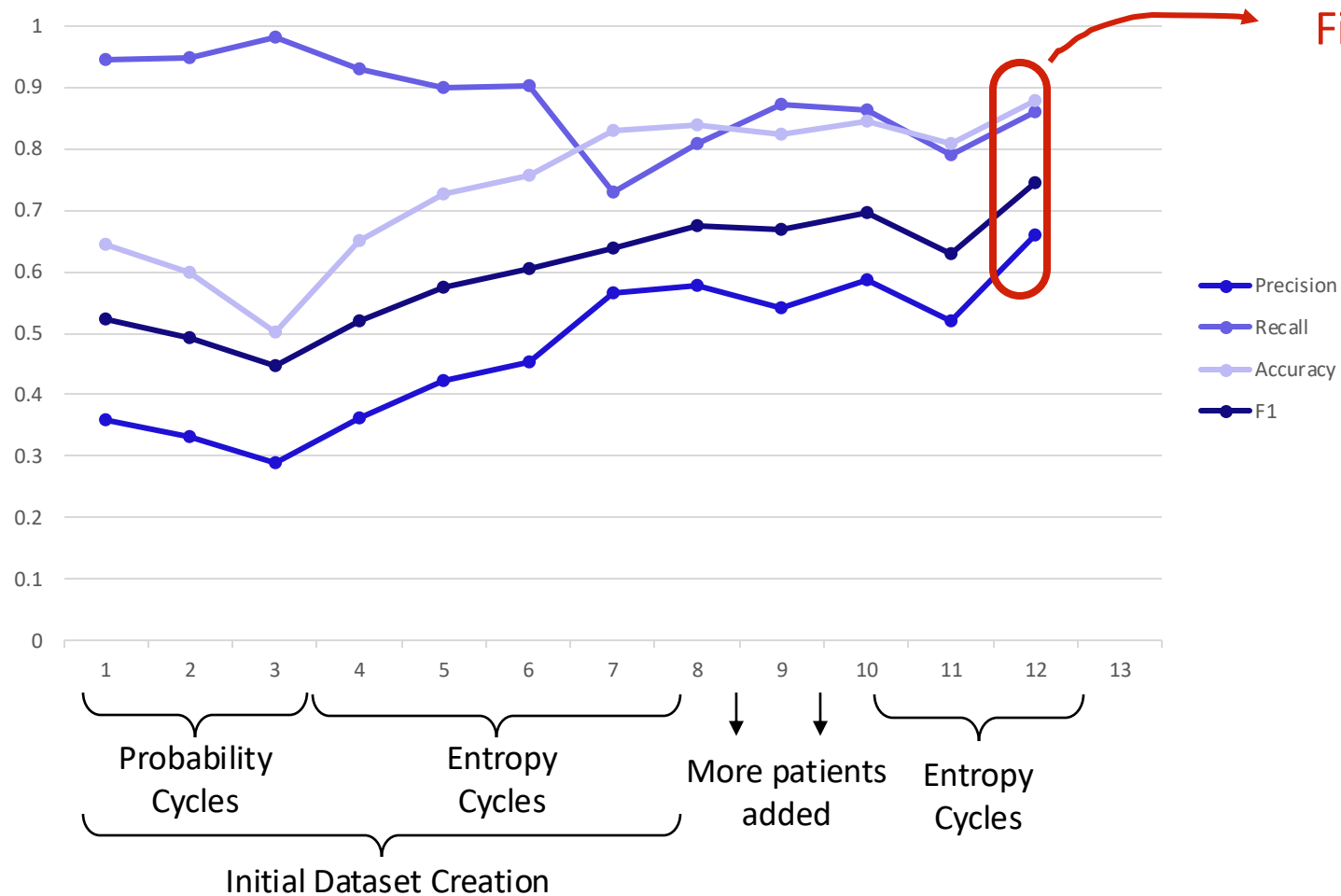
	Train		Validation		Test	
	Positive	Negative	Positive	Negative	Positive	Negative
Base Initial Dataset	178	220	43	61	164	174
Expanded Initial Dataset	428	2489	62	1026	476	1765

- Now, we can include more variability by adding images from more patients.

Active Learning



Results - iterations

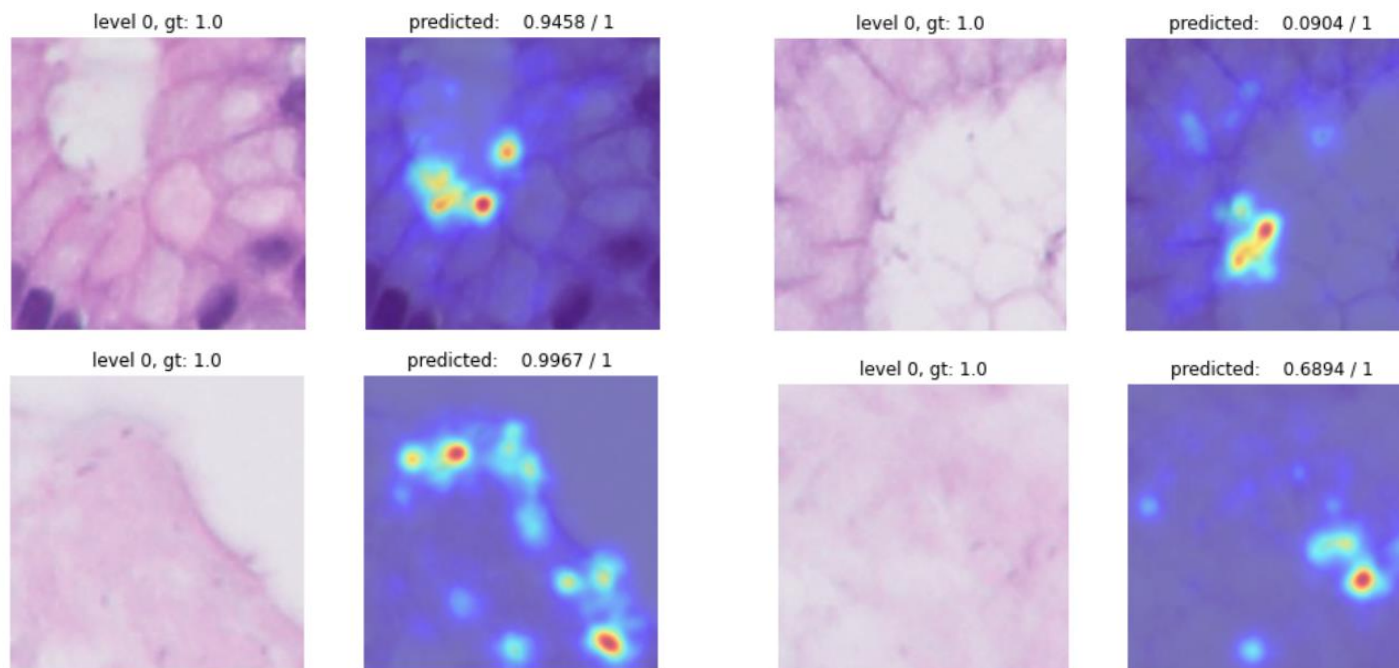


Final Model

Metrics calculated for each model in the final dataset (to allow comparison)

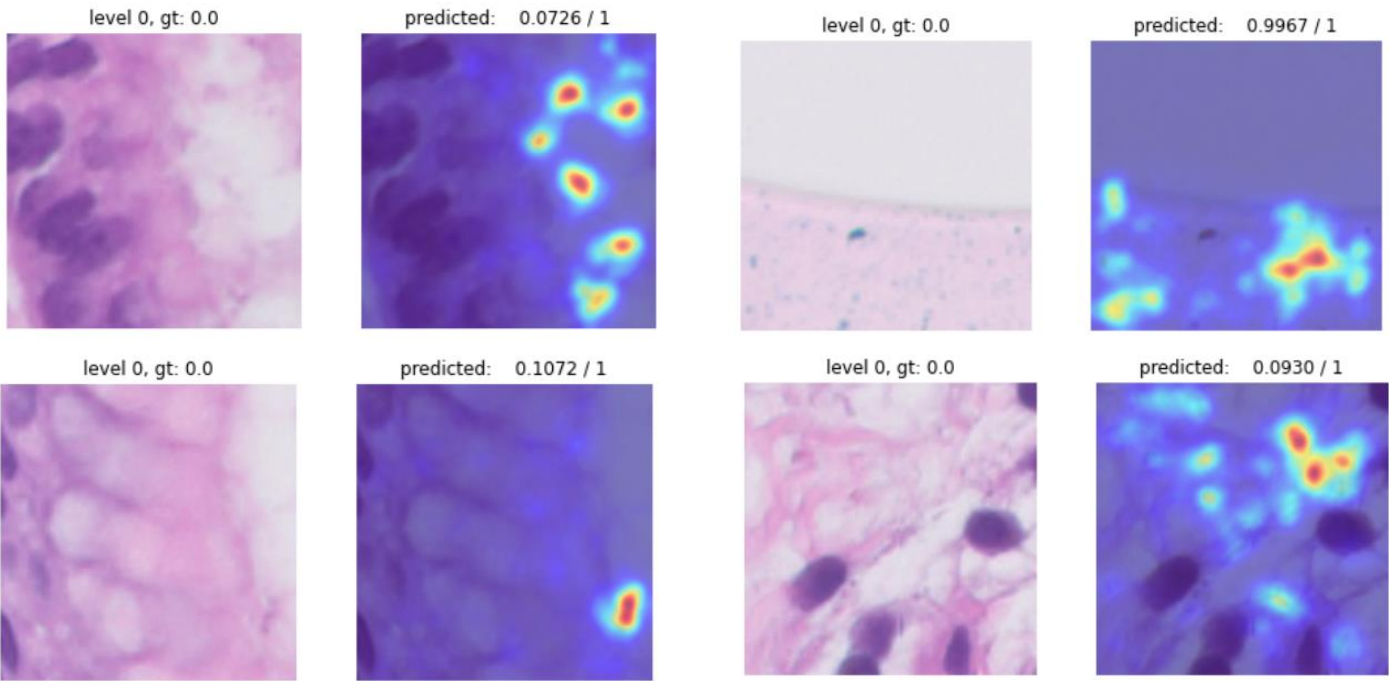
Results – Final Model

AUC	Precision	Recall	Accuracy	F1 Score
0.9467	0.6582	0.861	0.8796	0.746



Results – Final Model

AUC	Precision	Recall	Accuracy	F1 Score
0.9467	0.6582	0.861	0.8796	0.746



Results – Post Processing

	AUC	Precision	Recall	Accuracy	F1 Score
Before Post-Processing	0.9467	0.6582	0.861	0.8796	0.746
After Post-Processing	-	0.7807	0.7617	0.9071	0.8811

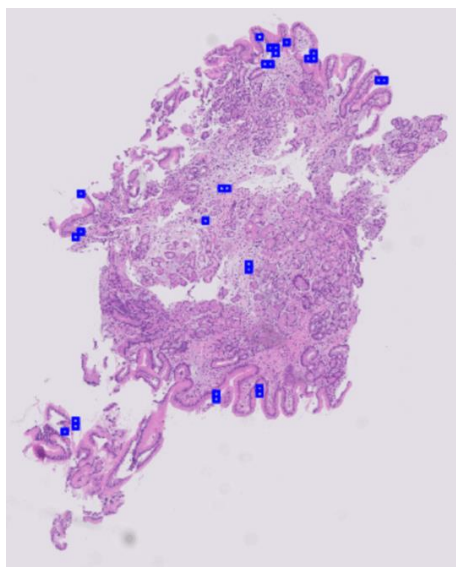
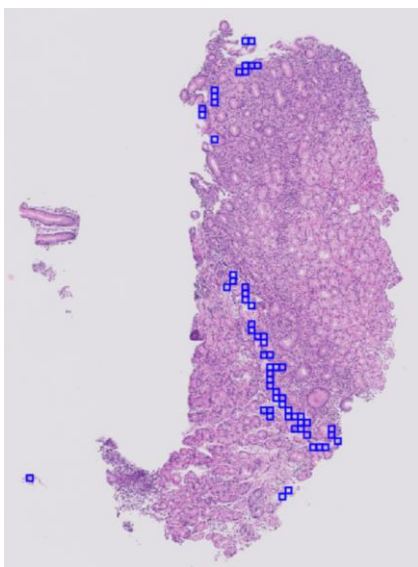
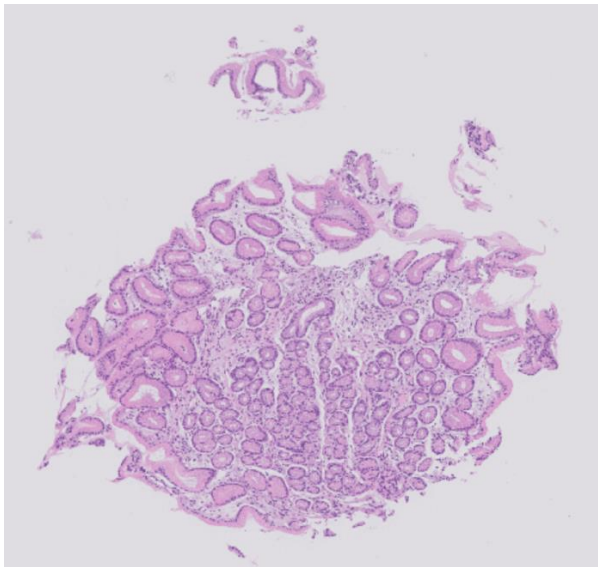
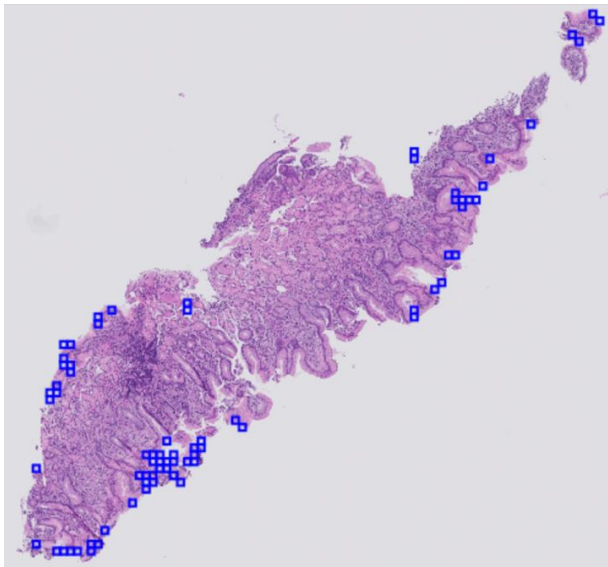
Removing patches with the following conditions:

- No positive patches in its direct neighborhood
- Probability less than 10 times the optimal threshold

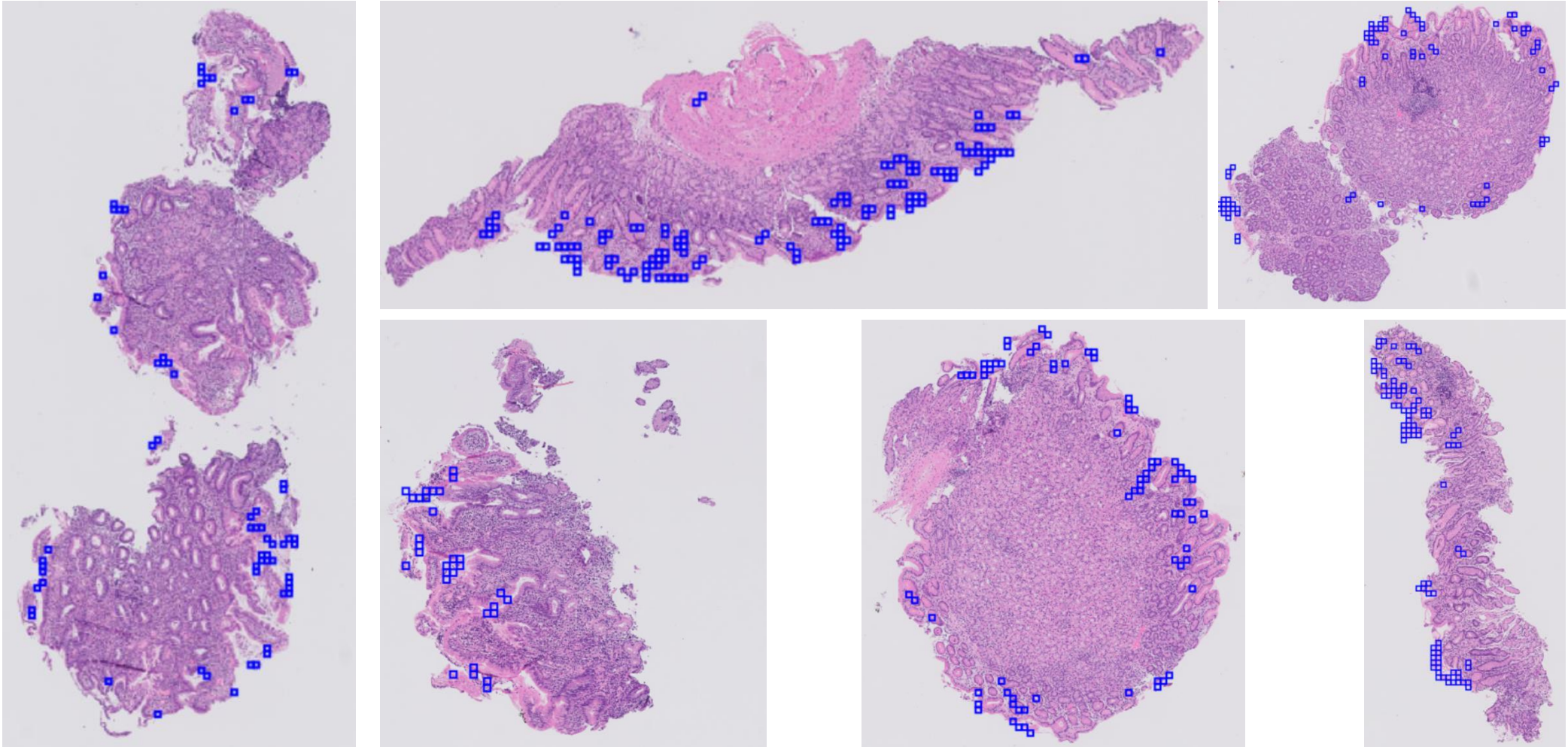
This way, isolated patches with lower probabilities are considered negative after post-processing

Results – Post Processing

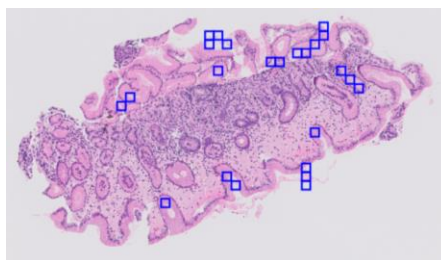
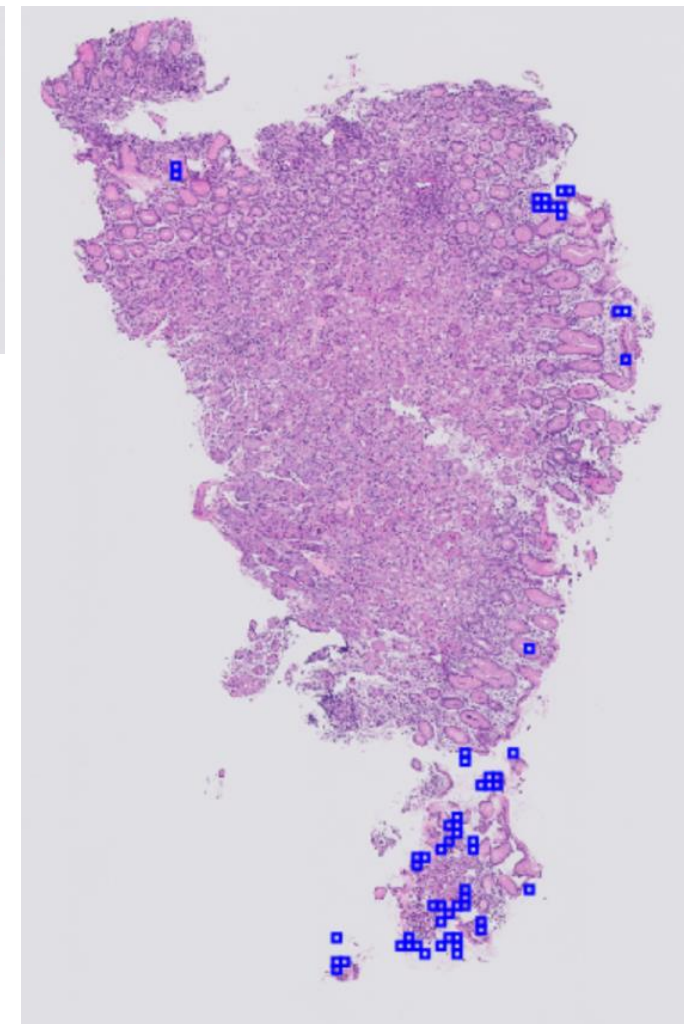
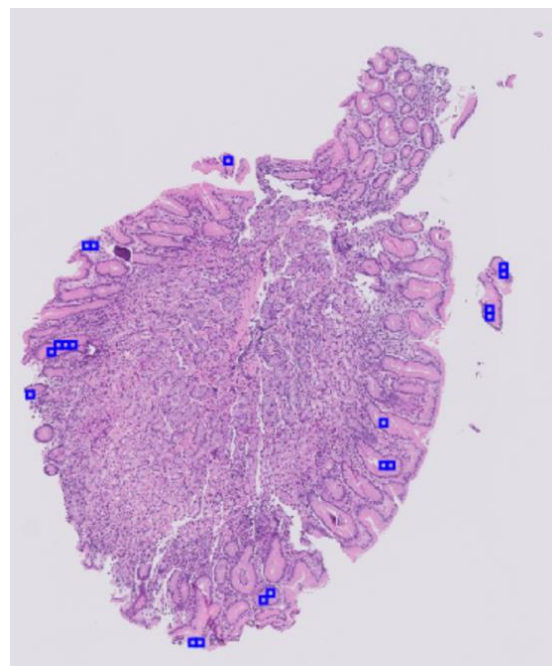
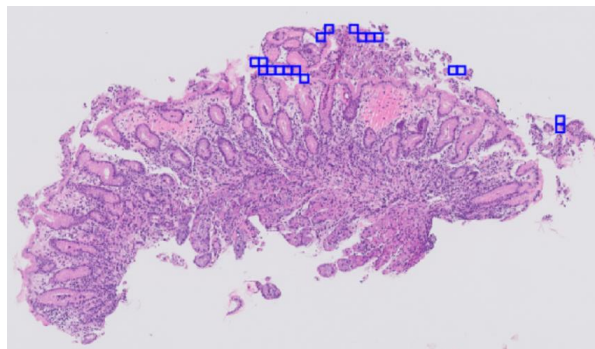
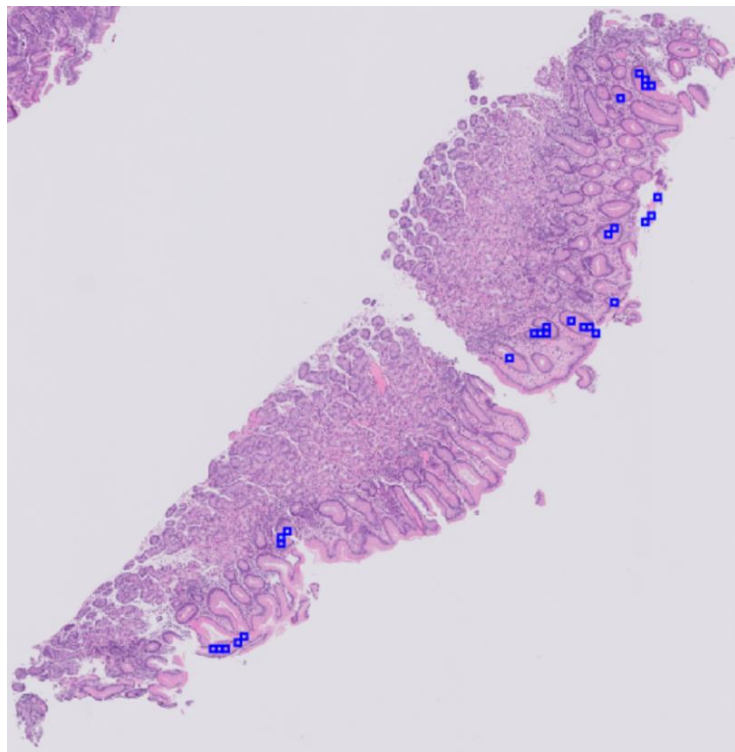
	AUC	Precision	Recall	Accuracy	F1 Score
Before Post-Processing	0.9467	0.6582	0.861	0.8796	0.746
After Post-Processing	-	0.7807	0.7617	0.9071	0.8811



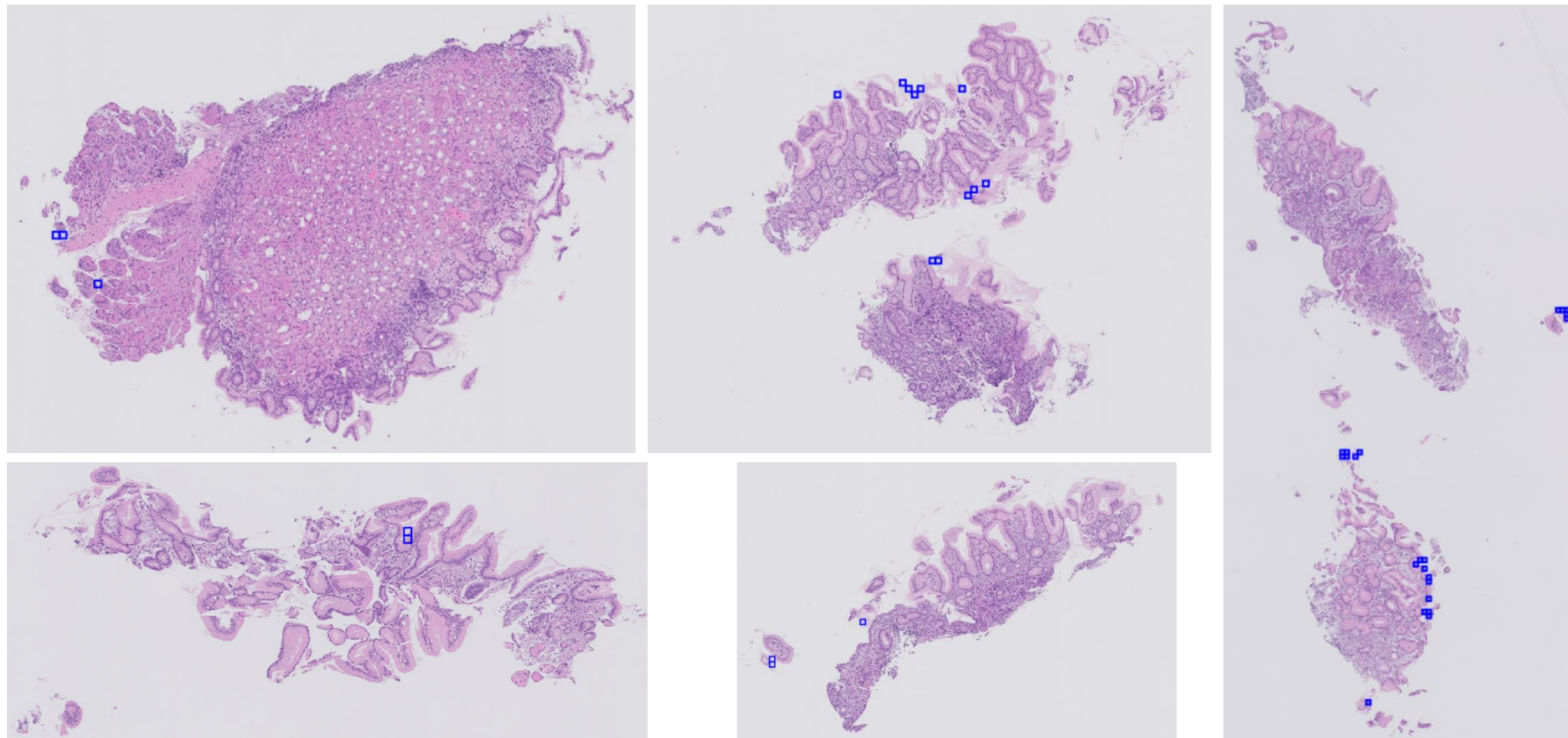
Results – Final Model – Examples of 3+ slides



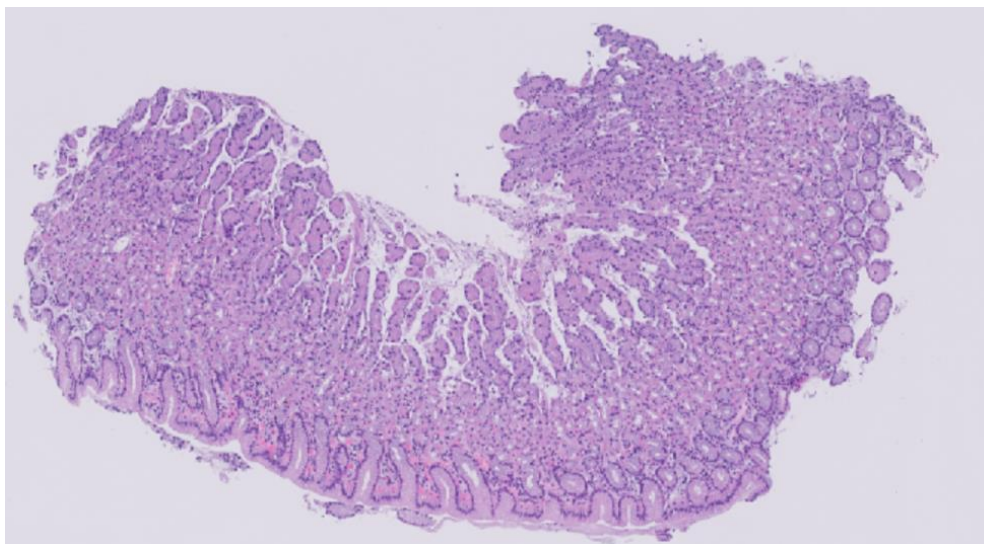
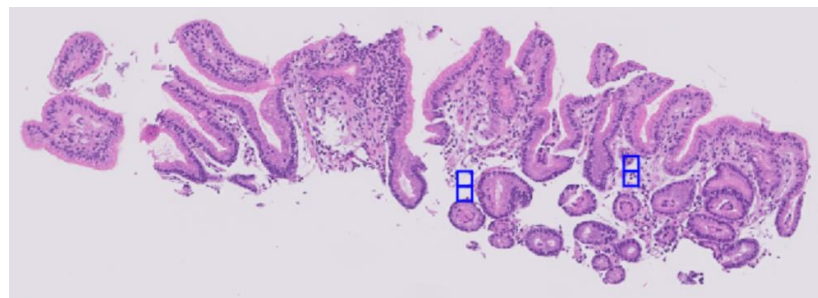
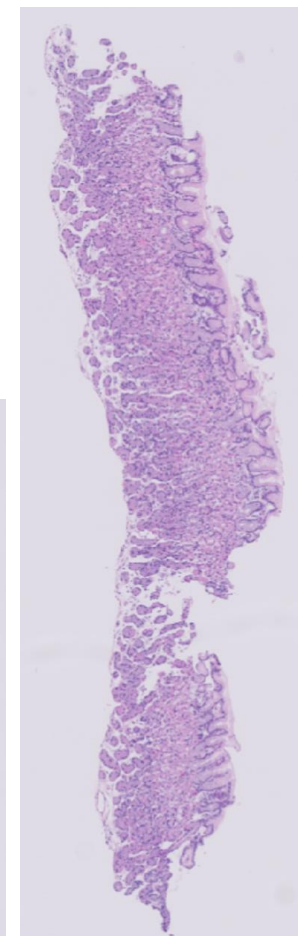
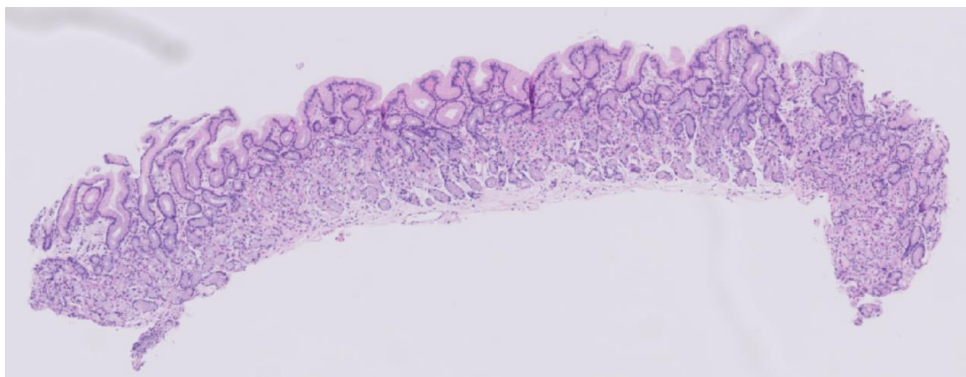
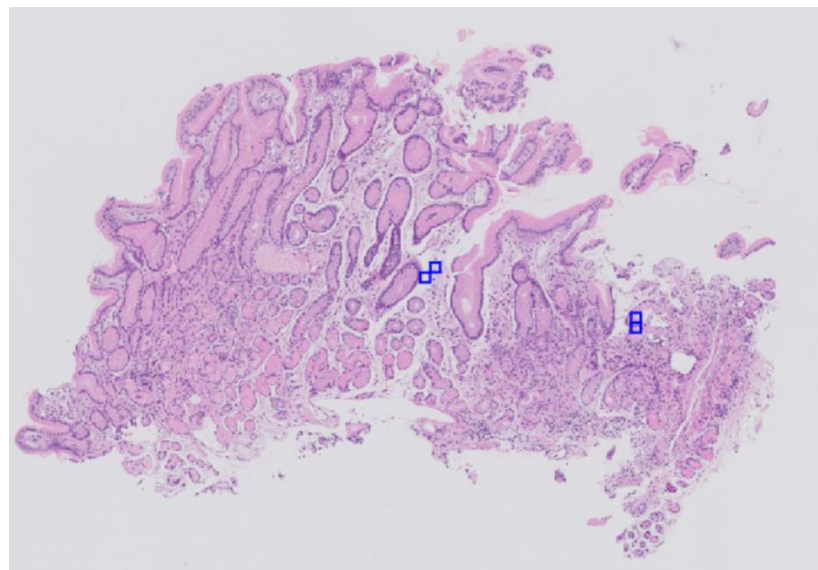
Results – Final Model – Examples of 2+ slides



Results – Final Model – Examples of 1+ slides

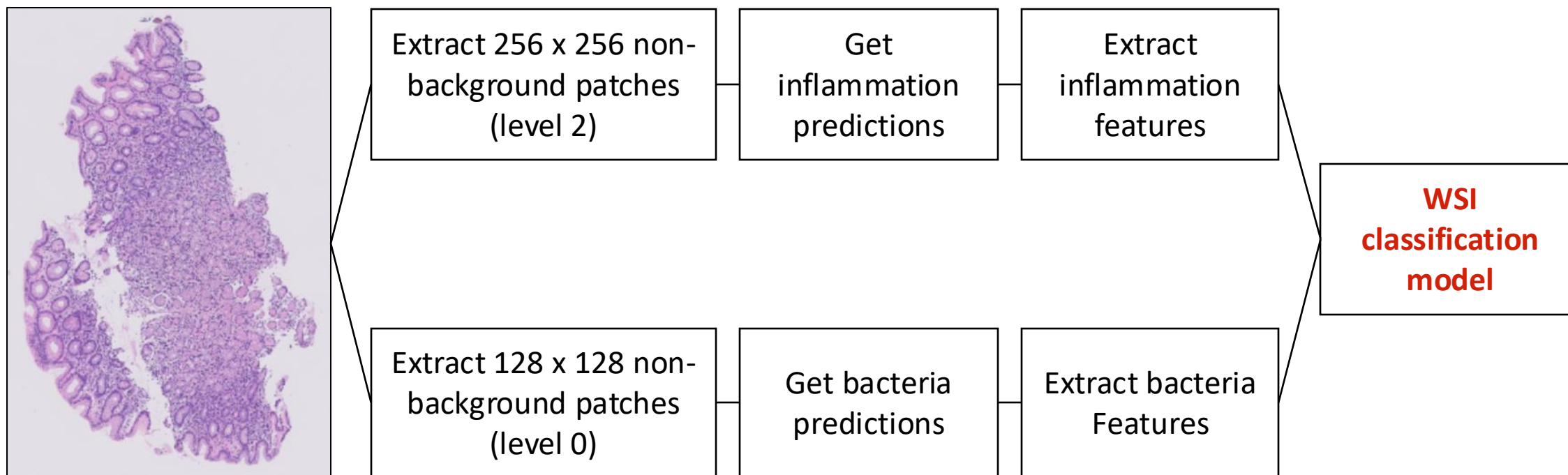


Results – Final Model – Examples of 0 slides



WSI Classification





WSI features

Inflammation features:

- Percentage of patches in each decile of probabilities
- Percentage of positive inflammation patches

Bacteria features:

- Percentage of patches in each decile of probabilities
- Percentage of positive bacteria patches
- Percentage of positive bacteria patches in groups (with at least 1 other positive patch in its direct neighborhood)
- Average number of positive patches in a group, normalized by the total number of patches
- Maximum number of positive patches in a group, normalized by the total number of patches

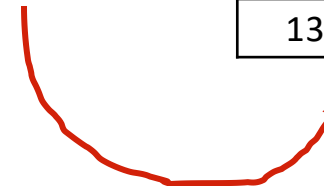
WSI Model – regression

Inflammation
Features

Bacteria
Features

	Decision Tree Regression	Random Forest Regression	Gradient Boosting Regression
Mean Squared Error (MSE)	0.3571	0.3181	0.2782
Root Mean Squared Error (RMSE)	0.5976	0.5640	0.5274
Mean Absolute Error (MAE)	0.3571	0.4293	0.3699
R-squared (R^2)	0.7348	0.7638	0.7935
Bias	0.2143	0.1621	0.2144

Slide	GT*	Pred
0	3	2.988287
1	0	0.207243
2	0	0.239360
3	2	2.007066
4	2	2.999600
5	2	2.001471
6	0	0.121269
7	3	2.943030
8	0	0.717454
9	1	0.120298
10	1	1.975565
11	0	0.743773
12	1	1.099693
13	3	2.958682



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References

- [1] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952980/#:~:text=pylori%20causes%20chronic%20inflammation%20and,of%20cancer%2Drelated%20deaths%20worldwide.>
- [2] <https://www.researchgate.net/publication/358240628>
- [3] <https://journals.sagepub.com/doi/10.1177/1533033820946787?icid=int.sj-abstract.similar-articles.1>
- [4] https://journals.lww.com/ajsp/abstract/1996/10000/classification_and_grading_of_gastritis_the.1.aspx
- [5] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5727686/>