USING DEEP LEARNING TO PREDICT OVERALL SURVIVAL TIMES FOR BREAST CANCER FROM H&E-STAINED WHOLE SLIDE BIOPSY IMAGES

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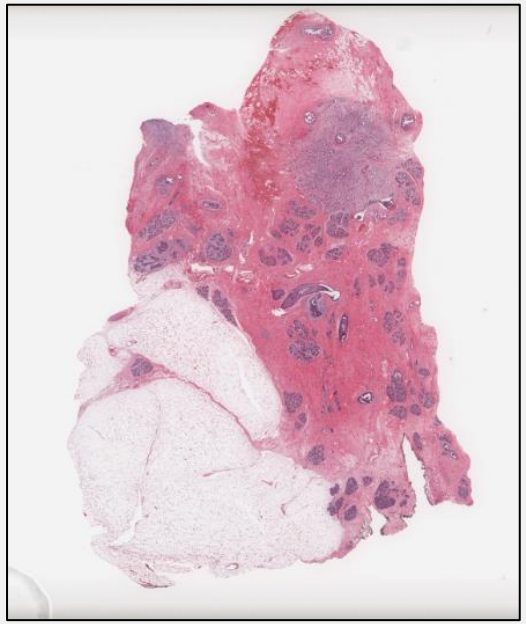
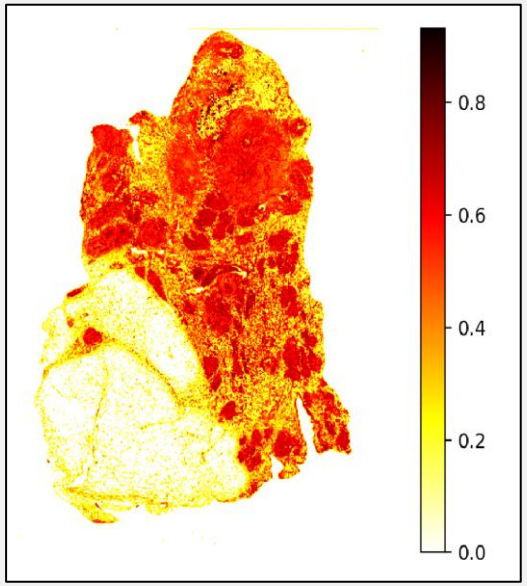
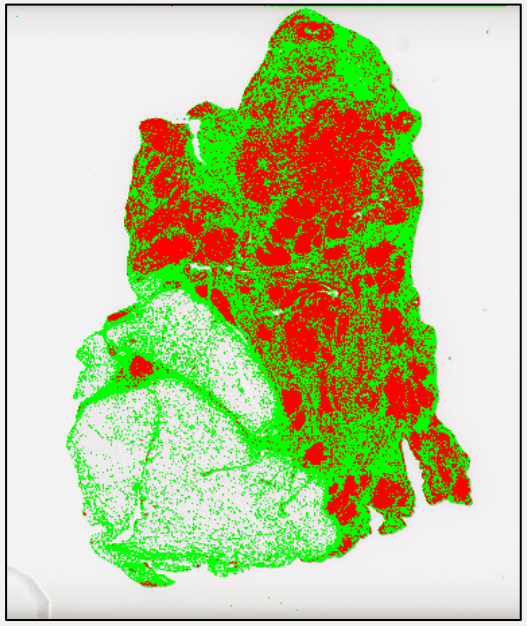


Breast tissue biopsy slide image

Classification



Mean Malignant Intensity



Malignancy Spread Score

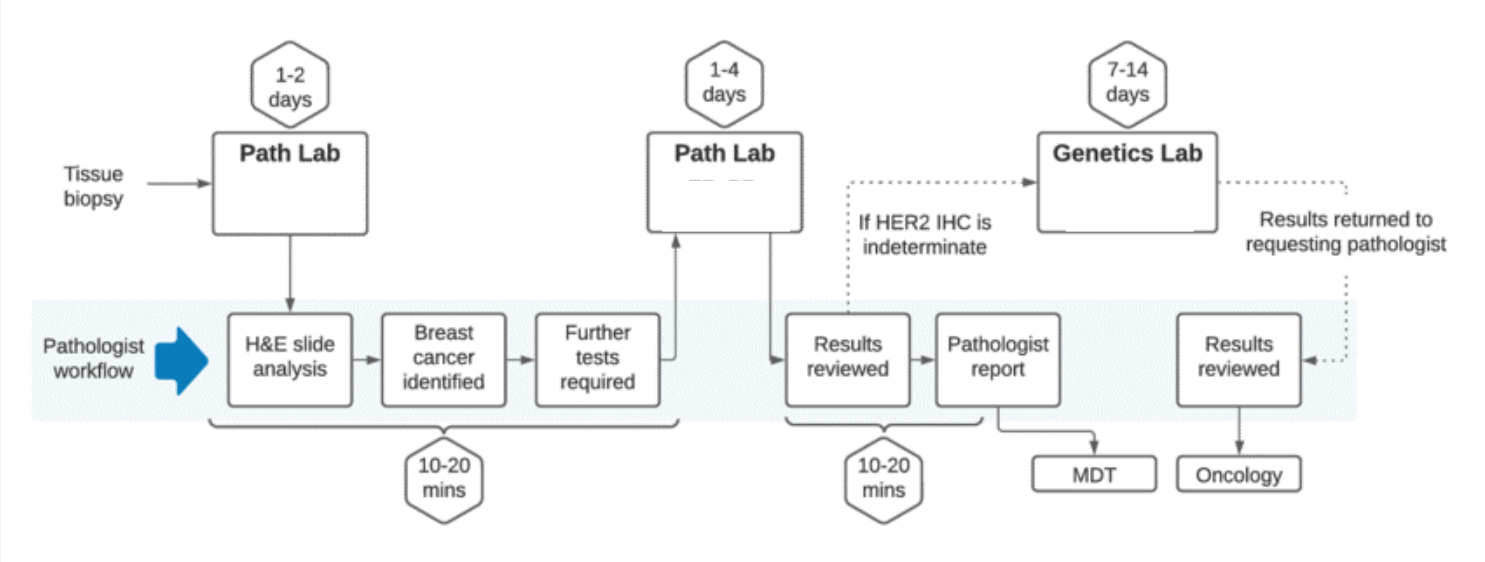
Regression

Survival Duration (months)	Predicted survival (months)
76.47	51.35

Survival Prediction

WHAT IS THE MOTIVATION BEHIND DOING OUR PROJECT?

Diagnostic workflow

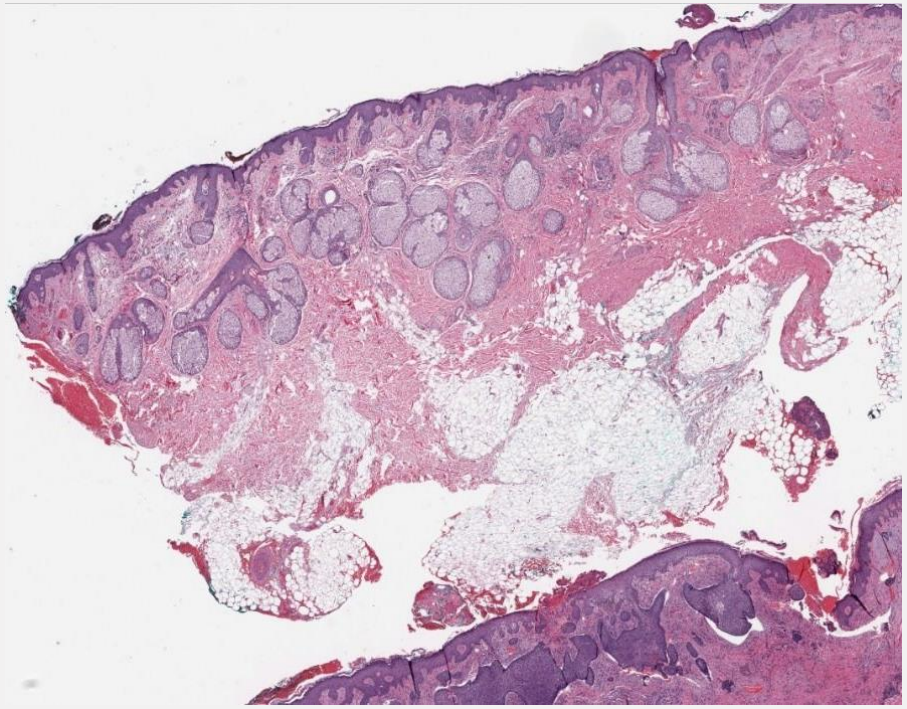


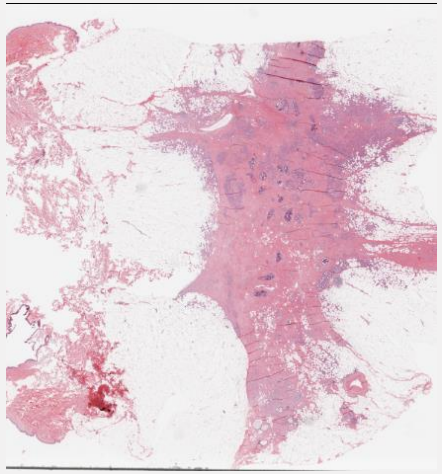
Clinical data collected for prognosis estimation

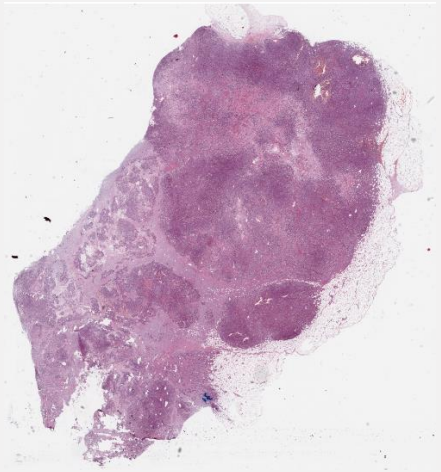
Patient ID	Sample ID	Cancer Study	Cancer Type	Cancer Type Detailed	Number of Samples Per Patient	Mutation Count	Fraction Genome Altered	Diagnosis Age	MSI MANTIS Score	MSIsensor Score	Sample Type	Sex	Ethnicity Category	Race Category	Subtype	Tumor Type	Aneuploidy Score	Birth from Initial Pathologic Diagnosis Date	Buffa Hypoxia Score	ICD-10 Classification
TCGA-OR-A5J1	TCGA-OR-A5J1-01	acc_tcga_pan_can_atlas_2018	Adrenocortical Carcinoma	Adrenocortical Carcinoma	1	23	0.0585	58	0.275	0	Primary	Male		White	ACC	Adrenocortical Carcinoma, Usual Type	2	-21496		C74.0
TCGA-OR-A5J2	TCGA-OR-A5J2-01	acc_tcga_pan_can_atlas_2018	Adrenocortical Carcinoma	Adrenocortical Carcinoma	1	29	0.4033	44	0.3236	1.57	Primary	Female	Hispanic Or Latino	White	ACC	Adrenocortical Carcinoma, Usual Type	10	-16090		C74.0

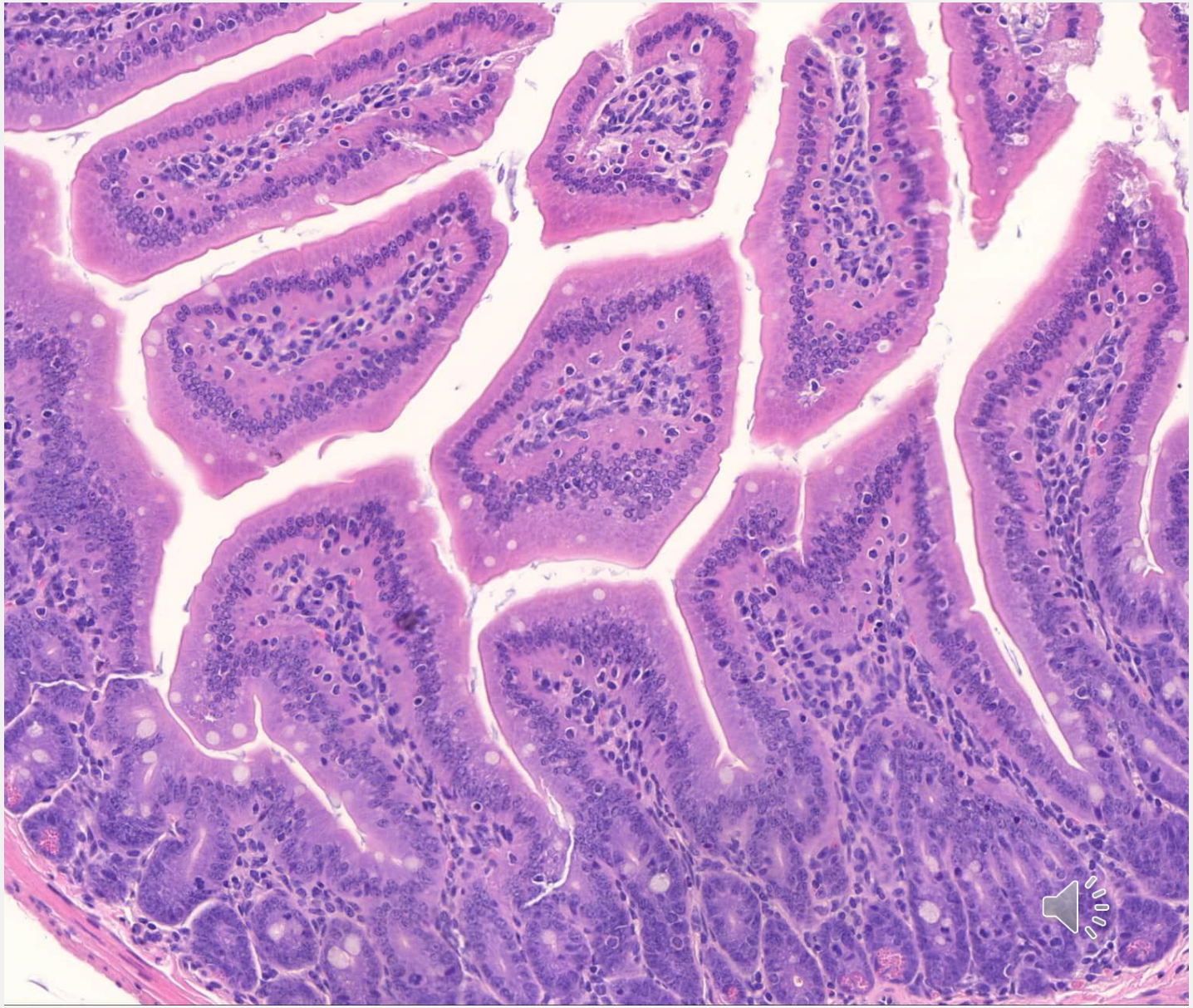
Neoplasm Histologic Grade	New Neoplasm Event Post Initial Therapy Indicator	Patient Weight	Person Neoplasm Cancer Status	Primary Lymph Node Presentation Assessment	Prior Diagnosis	Radiation Therapy	Ragnum Hypoxia Score	Tissue Prospective Collection Indicator	Tissue Retrospective Collection Indicator	Tissue Source Site	Tumor Disease Anatomic Site	Winter Hypoxia Score
	Yes		With Tumor		No	No		No	Yes	University of Michigan	Adrenal Gland	

Whole Slide Images of biopsied tissue









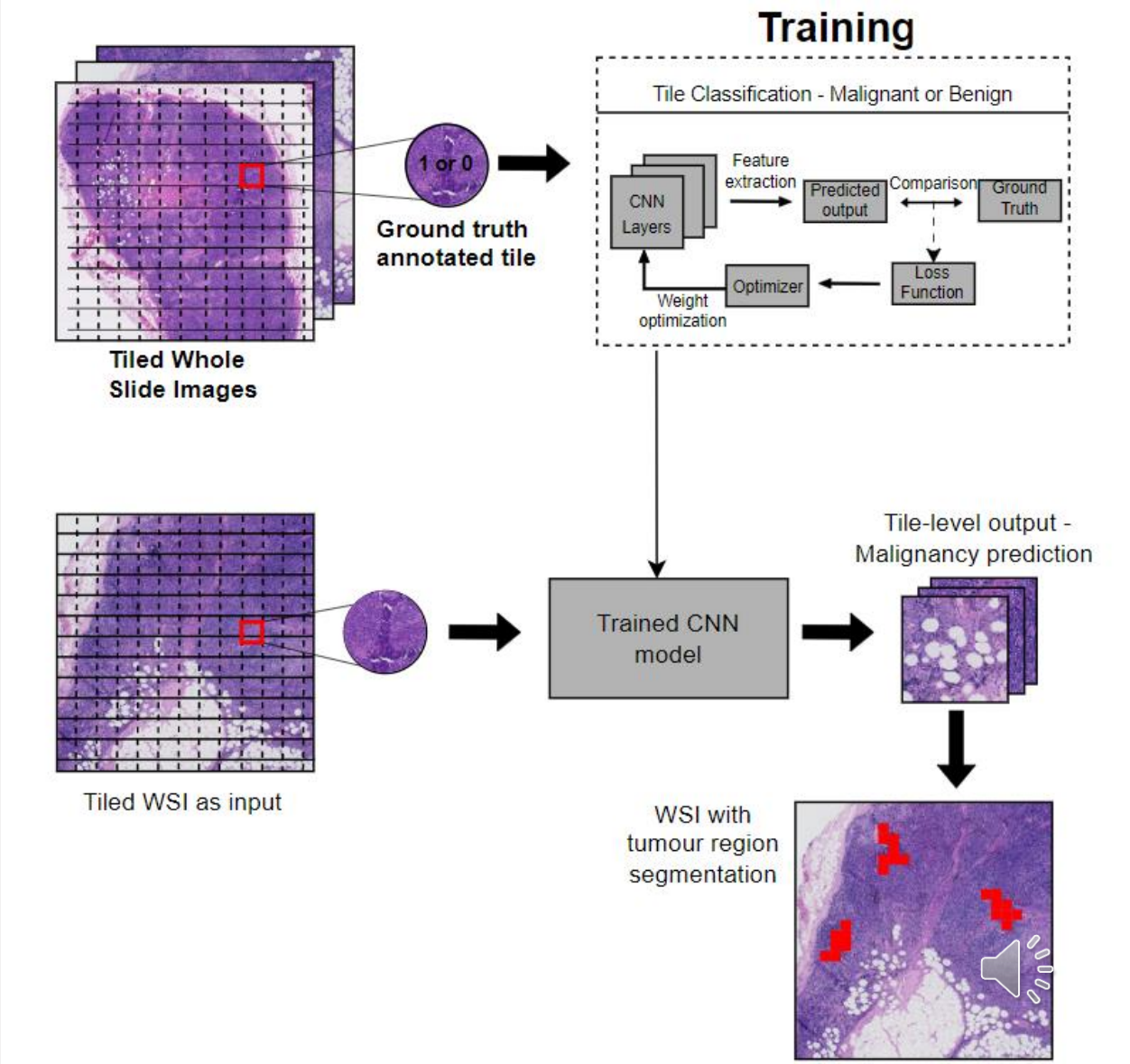
WHAT IS THE OVERALL PROBLEM WE ARE TRYING TO SOLVE ?

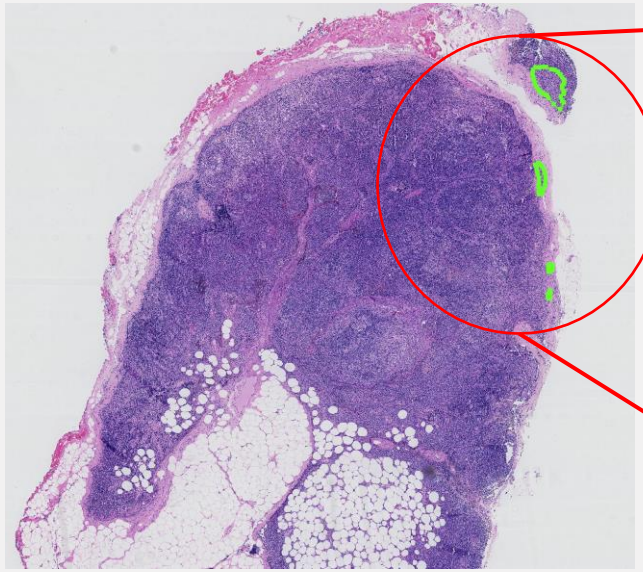
PROJECT AIMS

Can be broken down into two separate tasks:

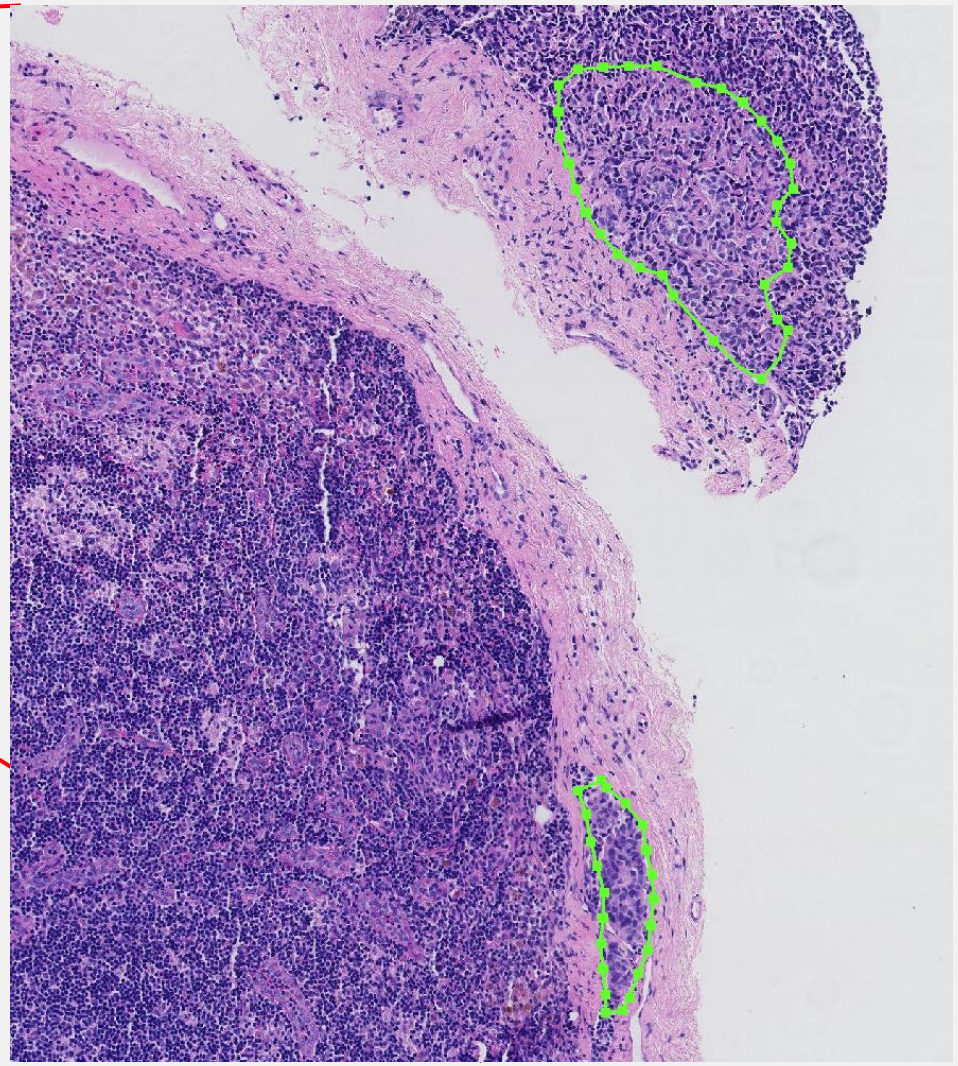
- Diagnostic stage – Identification of malignant tumor regions from H&E-stained whole slide images of breast tissue.
- Prognostic stage – Investigate the viability of whole slide images in estimating overall survival time of patients based on disease severity extracted from their biopsy image.

DIAGNOSTIC STAGE





Breast metastases annotated WSI; taken from Camleyon16 dataset.

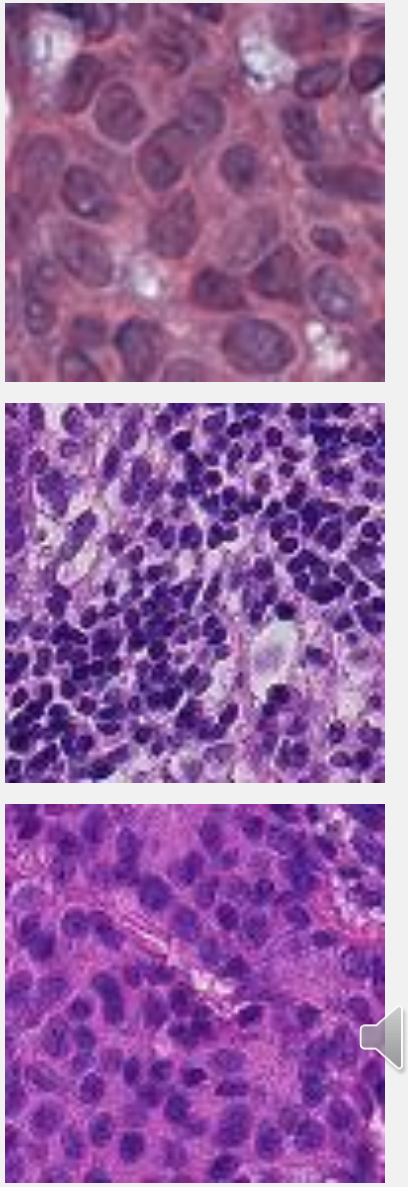


Core indicators of breast metastases:

- Abnormal nuclei growth indicative of regions showing larger Hematoxylin-stained nuclei.
- Lower nuclei density and sparse Eosin-stained cytoplasmic regions

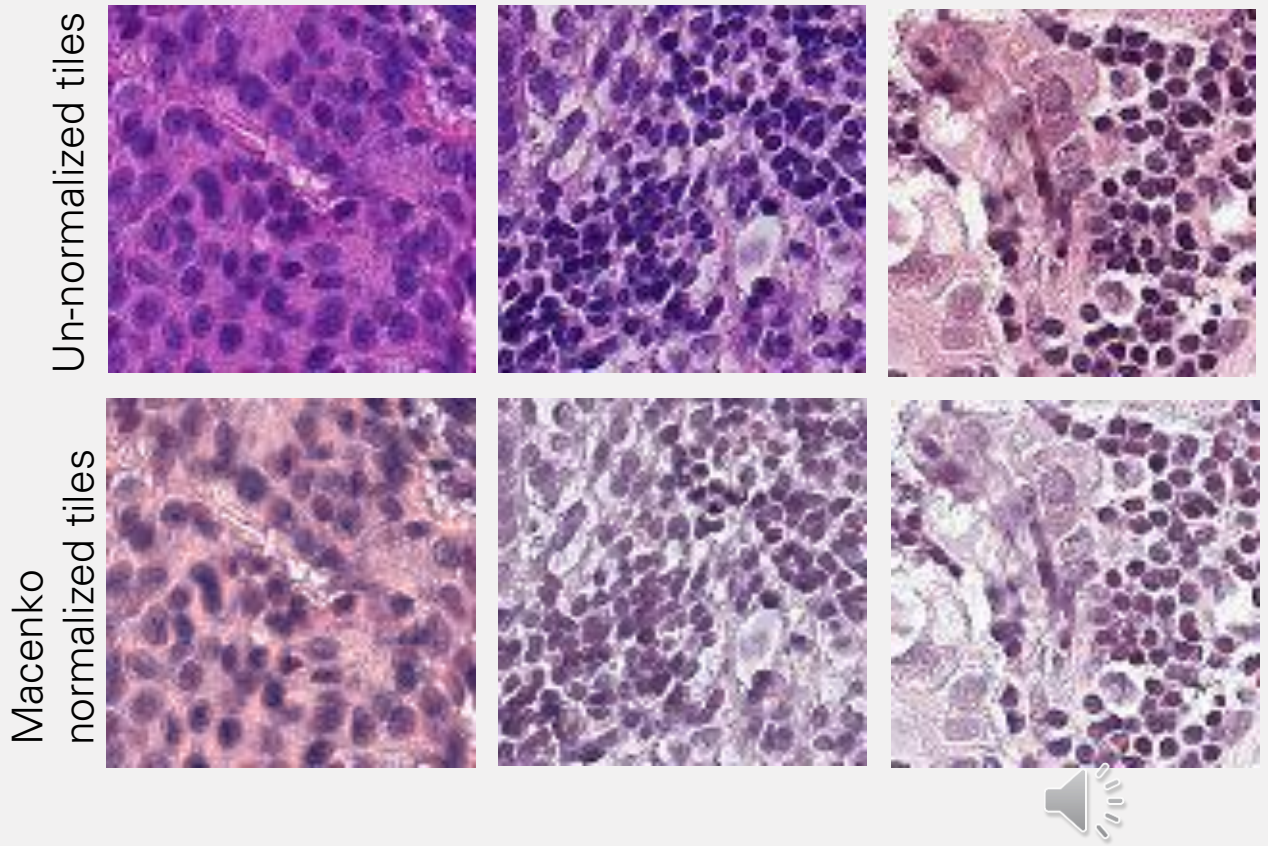
TRAINING DATA

- Lack of annotated breast cancer data. Infeasible to hire a pathologist and annotate our own dataset.
- We used PatchCamelyon (PCAM) dataset – derivative of Camelyon16 challenge data.
- Data contains samples of breast metastases in lymph node tissue.
- 399 WSIs from pathology labs in Netherlands tiled into 96x96 px patches. Each tile is labeled by pathologists with binary annotations (0: benign, 1: malignant)
- Balanced training, validation and test sets
- We use 100,000 training tiles and 20,000 test and validation tiles

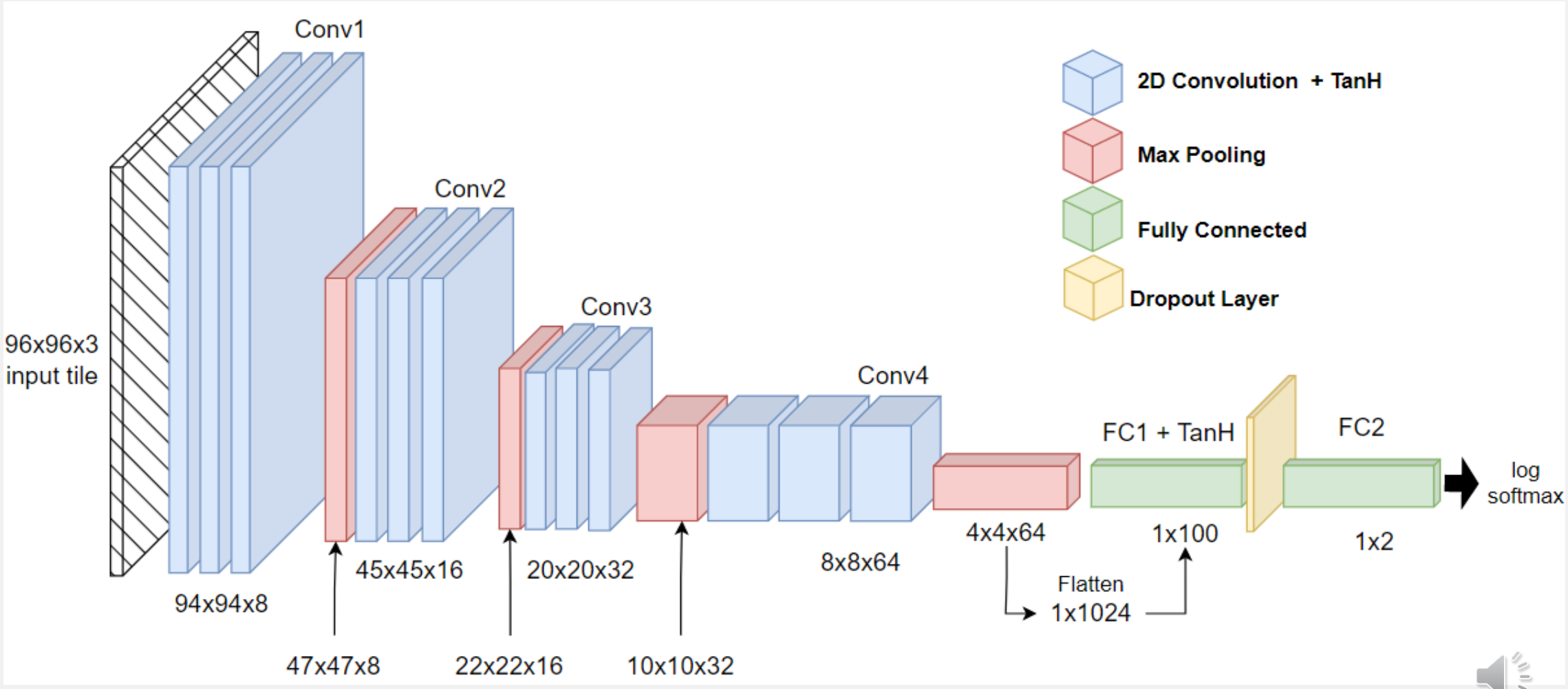


DATA PRE-PROCESSING

- Tiling
- Filtering background tiles
- Macenko normalization
- Augmentation



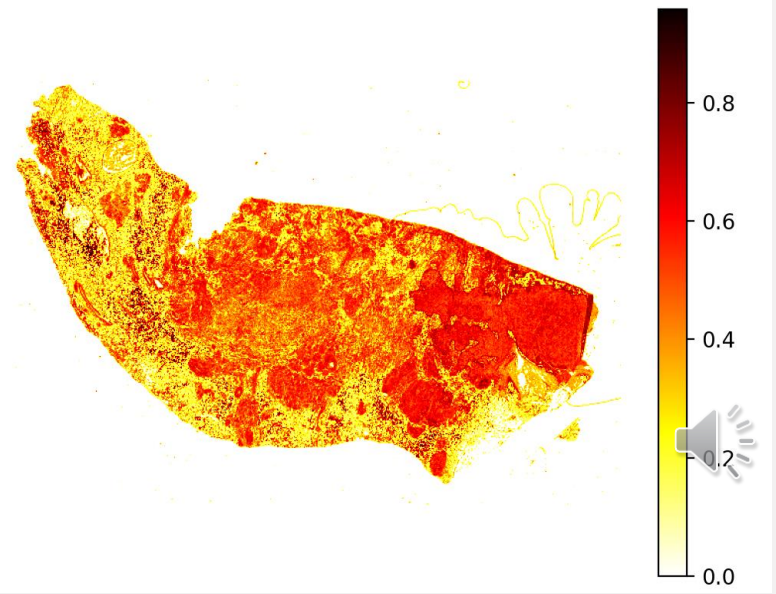
Neural network architecture:



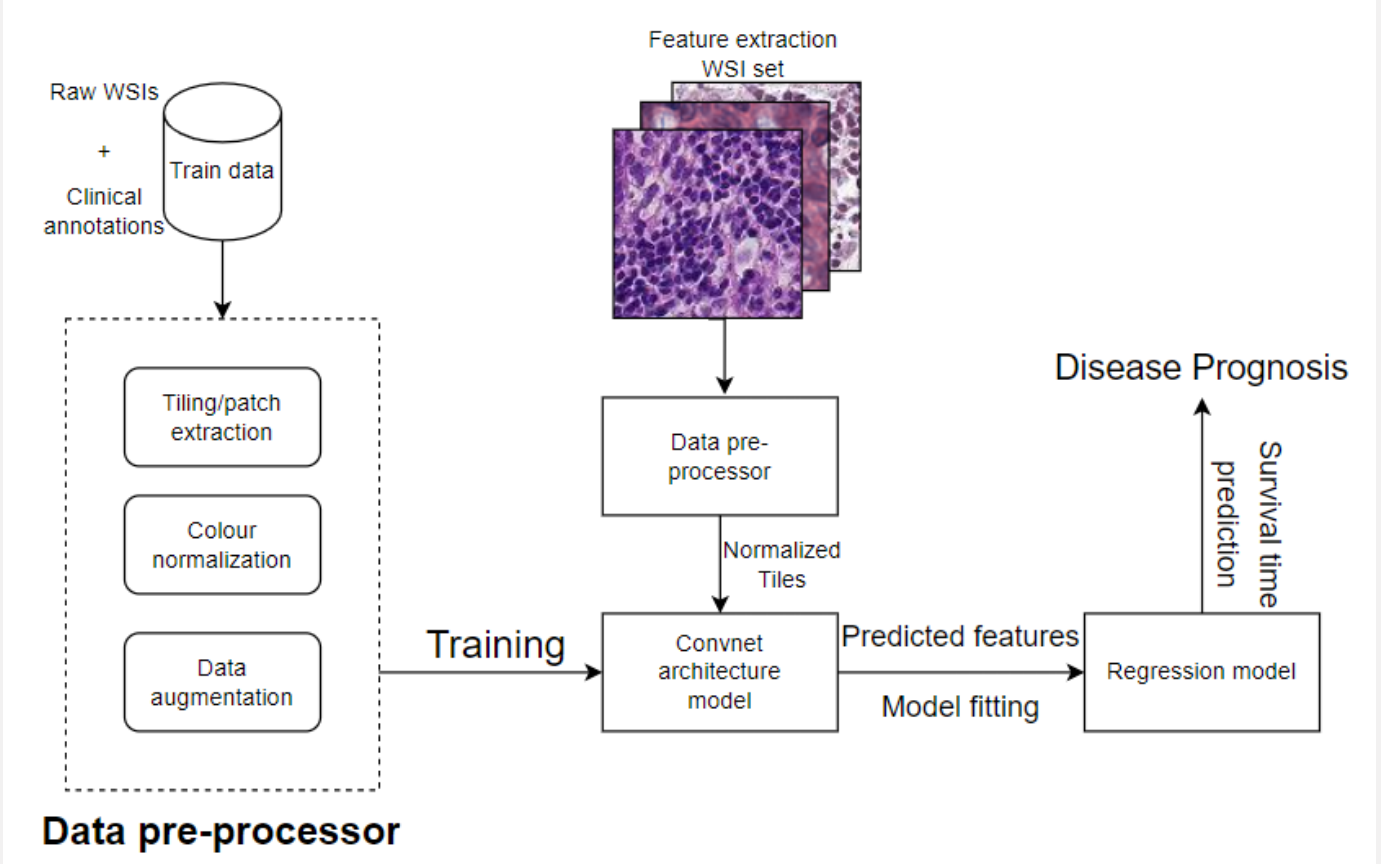
FEATURES EXTRACTED FROM SEGMENTED IMAGES

1. **Malignancy spread score** – Discrete binary predictions. Ratio of overall malignant area against total tissue surface area. Higher MSS indicates larger tumor spread and greater disease severity.

2. **Mean malignant intensity** – Continuous probability predictions. Average probability of malignancy across all tiles of a WSI. Higher MMI indicates more patches of strong malignancy translating to greater disease severity.



PROGNOSTIC STAGE



REGRESSION DATA

- Collect breast cancer WSIs of 74 patients from The Cancer Genome Atlas repository
- Retrieve each patient's associated survival duration – time from point of diagnosis to point of death to use as ground-truth in fitting our regression model
- Feed each WSI through pre-processor to split them into Maceko normalized tiles of dimension 96x96 px.
- Generate metastases predictions for each WSI using our trained model
- Calculate MMI and MSS covariate values for each of the 73 WSIs using the tile-level predictions
- Combine calculated covariates with the survival duration of each patient to get final regression dataset

Patient id	Survival duration	MMI score	MSS score
TCGA-BH-A1FE	76.47	0.67	0.75

COX PROPORTIONAL HAZARDS MODEL

$$\lambda(t|x) = \lambda_0(t) \exp(\beta_i x_i)$$

- $\lambda(t|x)$ is the hazard function
- t represents time.
- x_i denotes a vector for each covariate we use for our model.
- β is the regression coefficient vector calculated for our model.
- λ_0 is the baseline hazard under initial conditions x = 0
- Semi-parametric, linear regression model
- Gives us a hazard function that represents the hazard

KAPLAN-MEIER METHOD

$$\widehat{S}(t) = \prod_{i:\ t_i \le t} \left(1 - \frac{d_i}{n_i}\right)$$

- S(t) is the survival function
- t is the given time at which we want to estimate survival probability
- For each time t_i we calculate the ratio between the number of deaths that take place (d_i) and the number of subjects that survive at each time (n_i).
- Non-parametric statistical model
- Gives us the probability of survival past time t.
- Hazard Ratio $\exp(\beta_i x_i)$ from Cox model gives the probability of death at each point of time t_i

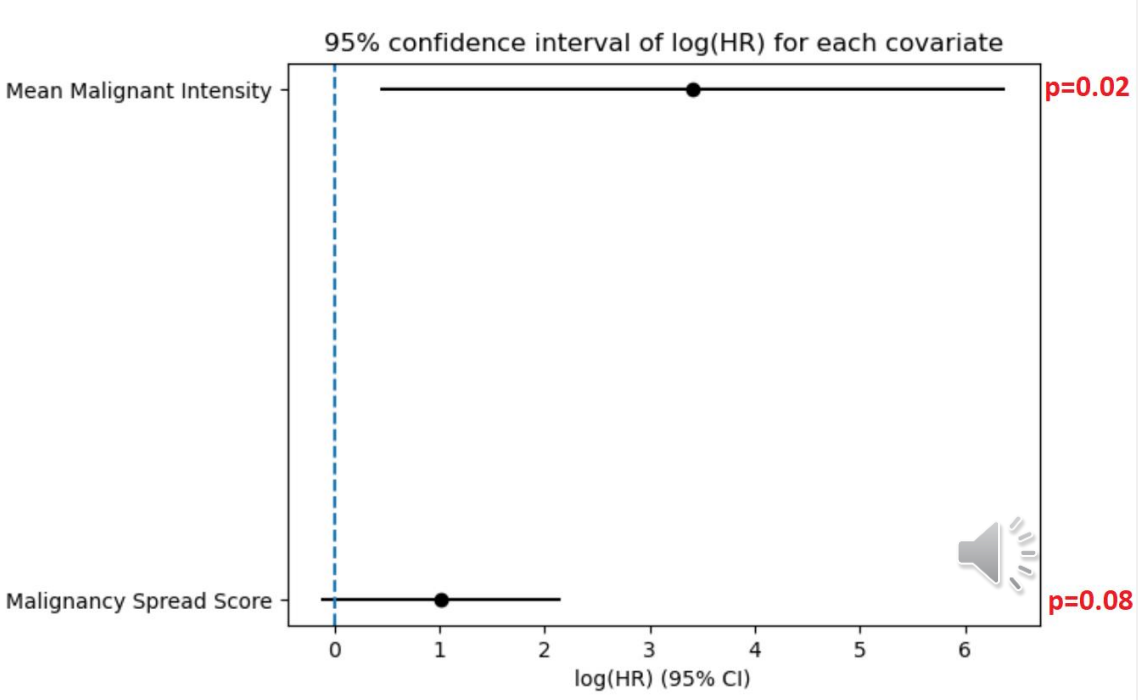
RESULTS

SURVIVAL MODEL FIT

Covariate	Exp(β)	z	p
MSS	2.78	1.76	0.08
MMI	30.20	2.25	0.02

- The HR value of both models is > 0 indicating both covariates are risk factors negatively effecting survival.
- HR of MMI is much higher than MSS implying the severity captured by that covariate has a much stronger correlation with disease hazard.
- MMI had a higher z-value than MSS indicating its β coefficient is more statistically different from 0 and has a stronger effect on patient survival.
- In survival modeling p<=0.05 is considered significnat
- Only the model fitted using MMI covariate showed statistically significant effect on patient survival (p=0.02).

- 95% Confidence intervals of each model
- MMI showed much larger confidence interval indicating more uncertainty in estimating the associated HR but shows statistical significance as null value of HR = 1 is not in the interval
- MSS has a shorter interval indicating greater precision in HR estimation but does not show significance as it fails to reject the null value.



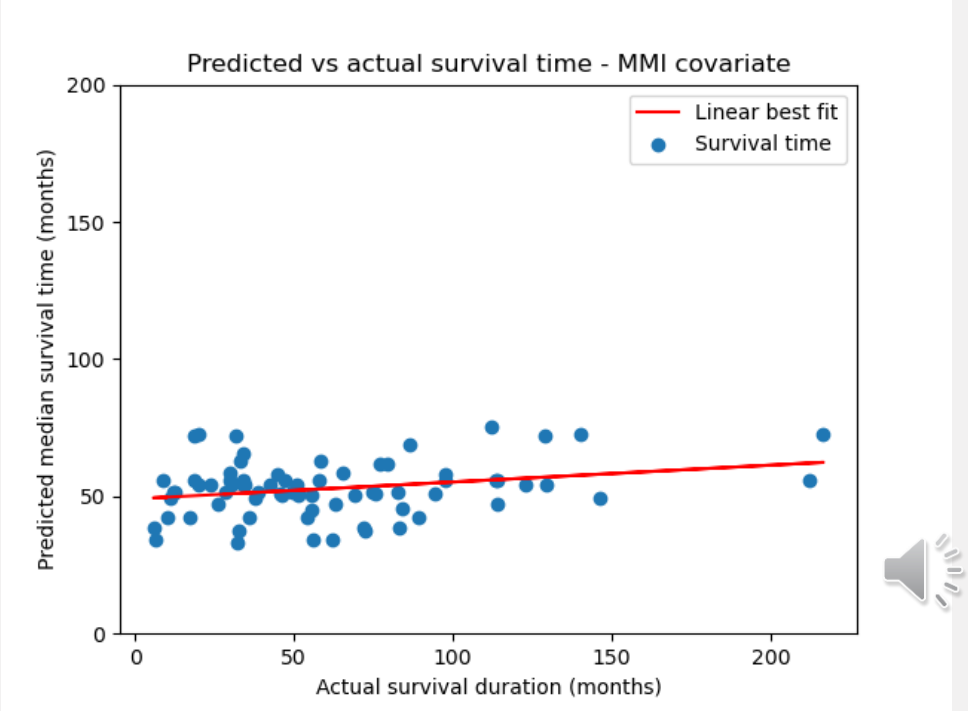
SURVIVAL TIME PREDICTION EVALUATION

- 5-fold cross validation results:

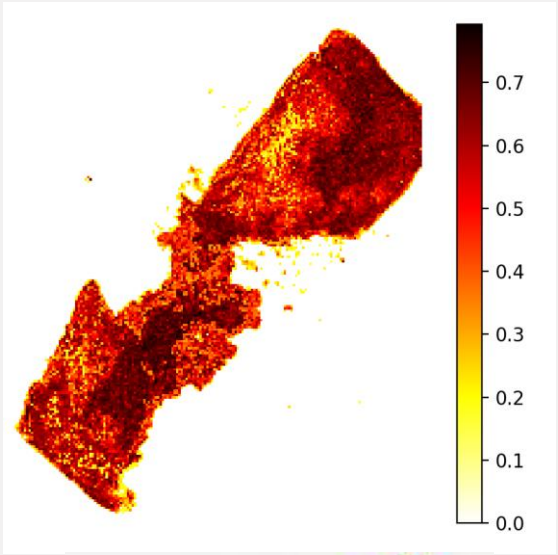
Covariate	Mean RMSE (months)	+/- Std deviation (months)
MMI	47.08	29.02
MSS	47.13	29.00

Likely reasons for poor performance:

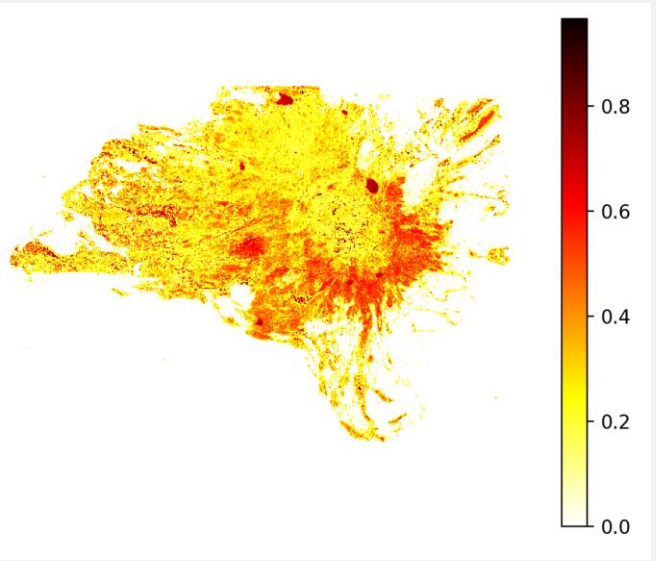
- Left censored data
- Patients' treatment regime is not known
- Access to healthcare - affordability and insurance access
- Smoking status, immune system health, underlying medical conditions, age etc.

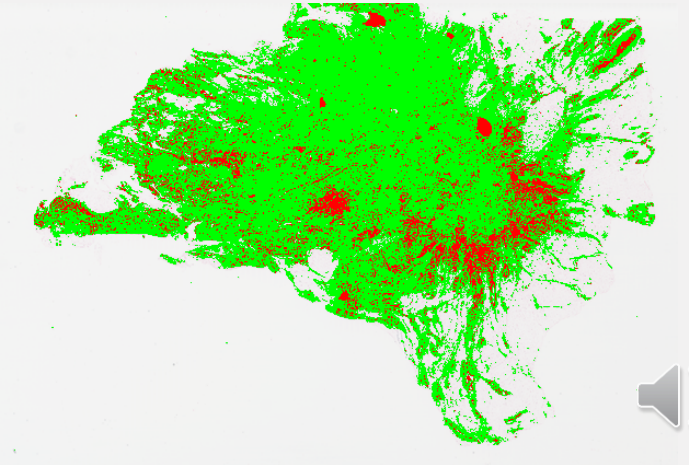


BREAST CANCER DETECTION PERFORMANCE - QUALITATIVE EVALUATION

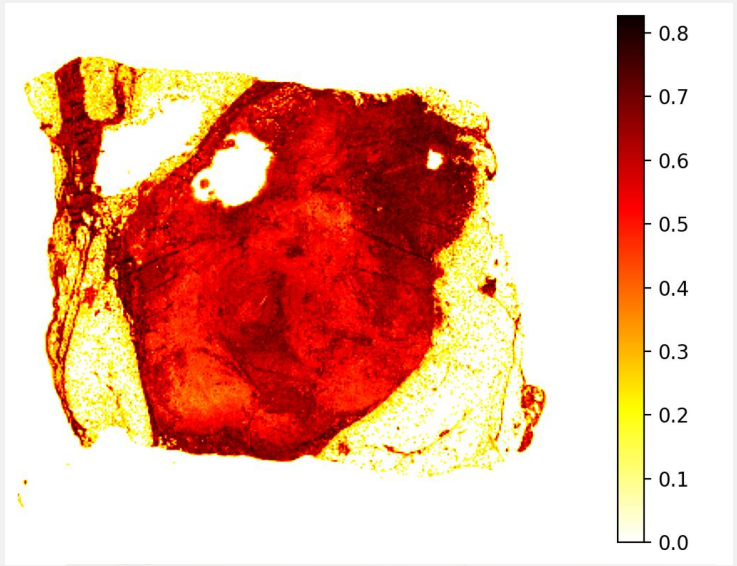


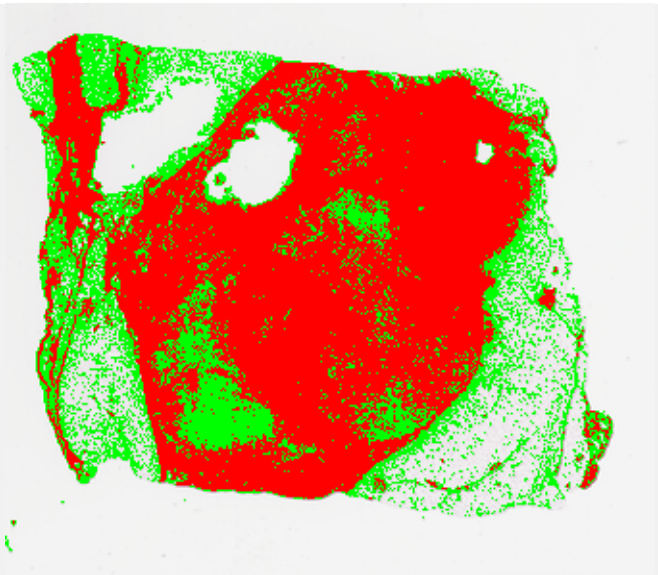
Recorded survival duration: 6.47 months



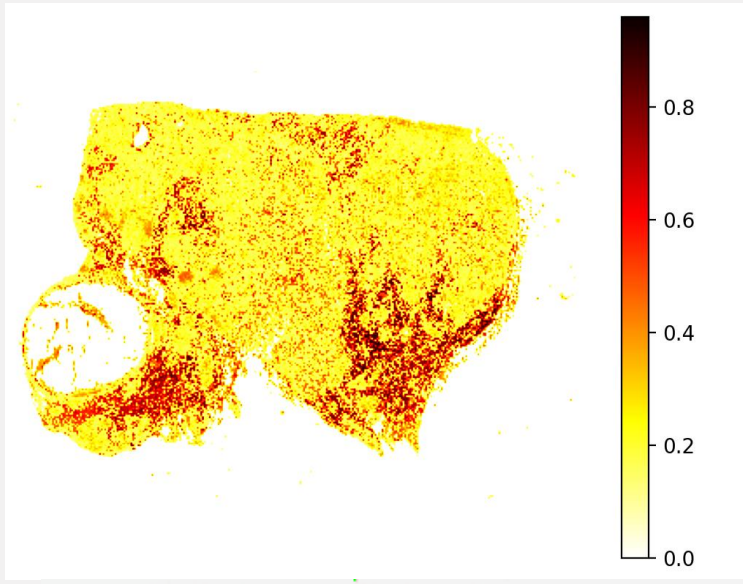


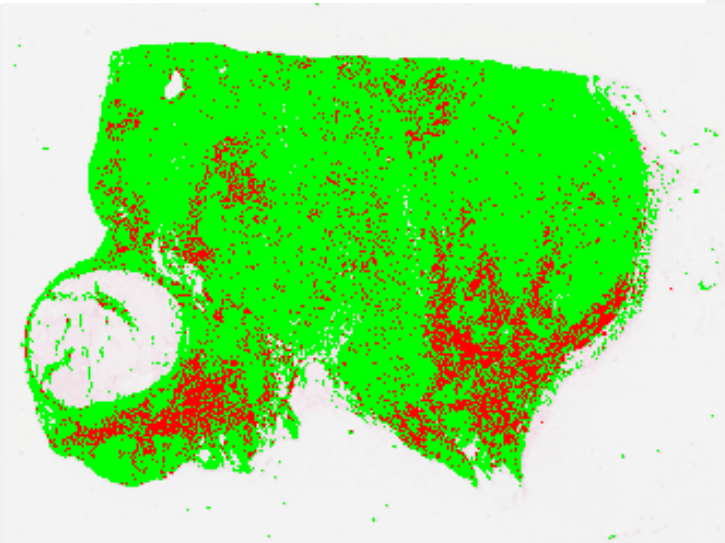
Recorded survival duration: 128.98 months





Recorded survival time: 17.21 months





Recorded survival time: 216.59 months

CONCLUSION

Diagnostic stage:

- Internal validation on PCAM data showed up 70% accuracy in malignancy classification.
- We qualitatively showed that the predicted metastases matches the corresponding survival duration recorded for each sample. High severity predictions correspond to low survival and vice versa.
- Learning of breast metastases acquired from lymph node tissue can be transferred to identify metastases in breast tissue to a reasonable degree.
- Future work: Can be improved using contextually appropriate data to train the model. An extension could be using weakly supervised learning instead of supervised learning approach to avoid needing annotated data.

Prognostic stage:

- Correlation between image-based features and patient survival was not strong enough to viably use WSIs in exact prognosis estimation without additional clinical data.
- This is because patient survival is influenced by several external factors, which univariate hazard models cannot characterize accurately.
- It can, however, predict the general trend in survival based on metastases severity which can provide a rough, initial baseline to allow prioritizing high-risk cases for treatment.
- Future work: Use multivariate models to extend hazard functions to be more realistic or use a different survival model like Aalen's additive hazards regression to model dynamic hazard using covariates that change with time.

THANK YOU

Project source code: https://github.com/AnirbitGhosh/L4-Project