CLASSIFYING CLINICALLY ACTIONABLE GENETIC MUTATIONS

CHEONG YU CHYE – DSI 13 – CAPSTONE PROJECT

OUR PROBLEM STATEMENT

- Cancer is a top public health issue[1]:
  - Globally, about 1 in 6 deaths is due to cancer
  - One in every 4-5 people in Singapore may develop cancer in their lifetime
- Today, clinical pathologists can perform genomic sequencing on a patient's tumour sample to determine if it carries mutations that could aid in treatment, or clinical trials[2]
- Once these genes and mutations (variations) have been identified, clinical pathologists manually review related biomedical literature to classify the mutations – this process is tedious and time consuming
- Our problem statement: to build a model that can help to automate this classification
  - Metrics: balanced (weighted) accuracy and F1 scores, micro-average AUC
  - Success measure: beat baseline accuracy (0.287) by ≥ 10%

Sources:
[1] - https://www.nccs.com.sg/patient-care/cancer-types/cancer-statistics, https://www.who.int/news-room/fact-sheets/detail/cancers
[2] - https://www.mskcc.org/cancer-care/diagnosis-treatment/diagnosing/role-pathology

THE CHALLENGE …

3,321 Training Samples

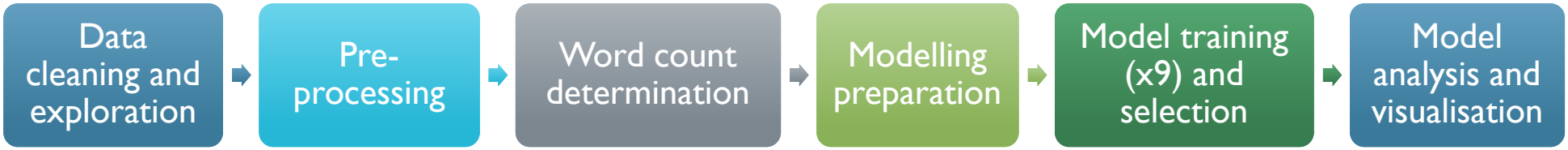
The incidence of breast cancer is increasing in China in recent decades, and familial breast cancer accounts for 5–10% of the total patients in Chinese women. Germline mutations in breast cancer susceptibility genes, BRCA1 (MIM# 113705) and BRCA2 (MIM# 600185), are responsible for only approximately 10% of Chinese breast cancer families [Liede and Narod, 2002]; …	+	CHEK2	+	H371Y	=	9
An unselected series of 310 colorectal carcinomas, stratified according to microsatellite instability (MSI) and DNA ploidy, was examined for mutations and/or promoter hypermethylation of five components of the WNT signaling cascade [APC, CTNNB1 (encoding β-catenin), AXIN2, TCF4, and WISP3] and three genes indirectly affecting this pathway [CDH1 (encoding E-cadherin), PTEN, and TP53]. APC and TP53 mutations were each present more often in microsatellite-stable (MSS) tumors ...	+	AXIN2	+	Q1537R	=	7

986 Test Samples

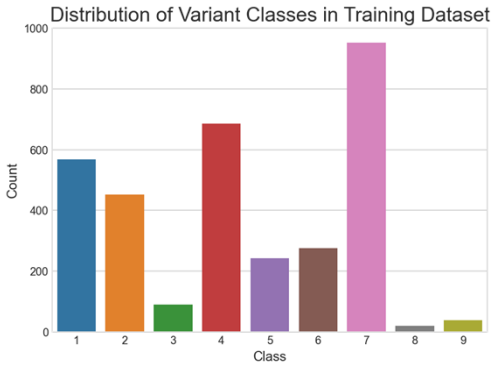
Mycosis fungoides and Sézary syndrome are primary cutaneous T cell malignancies derived from CD4+ skin-homing T cells1, 2. Mycosis fungoides cases with limited skin involvement have a favorable prognosis; however, the median survival time for cases with cutaneous tumors and generalized erythroderma is approximately 4 years, and patients with Sézary syndrome fare even worse …	+	WNT4	+	E216G	=	?
Regulated progression through the cell cycle requires sequential expression of a family of proteins called cyclins. Upon their induction, cyclins form complexes with specific cyclin-dependent kinases (CDKs), creating active holoenzymes that phosphorylate target proteins that are required for cell-cycle progression. Induction of the proto-oncogene cyclin D1, and its binding to …	+	GJB3	+	E183K	=	?

Legend: Clinical Text | Gene | Variation | Class

OUR APPROACH – AT A GLANCE



WHAT WE NOTICED



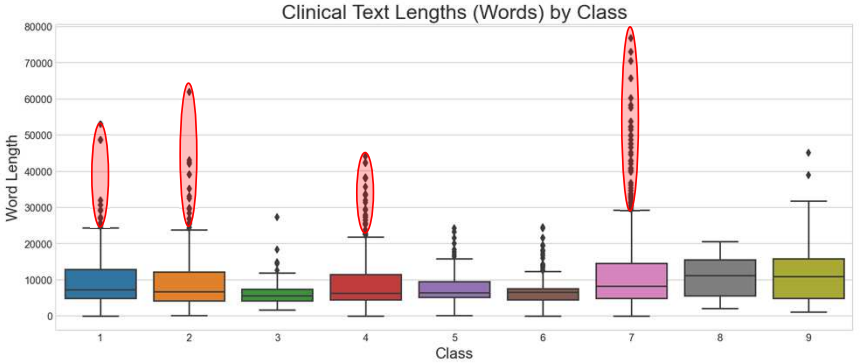
We have very imbalanced classes (especially class 7)

Average # of words

9,543

Maximum # of words

76,708



We decided not to remove any of the outliers given the importance of retaining as many words as possible for training our models

PREPARING THE CLINICAL TEXT FOR PROCESSING

An unselected series of 310 colorectal carcinomas, stratified according to microsatellite instability (MSI) and DNA ploidy, was examined for mutations and/or promoter hypermethylation of five components of the WNT signaling cascade [APC, CTNNB1 (encoding β-catenin), AXIN2, TCF4, and WISP3] and three genes indirectly affecting this pathway [CDH1 (encoding E-cadherin), PTEN, and TP53]. APC and TP53 mutations were each present more often in microsatellite-stable (MSS) tumors.

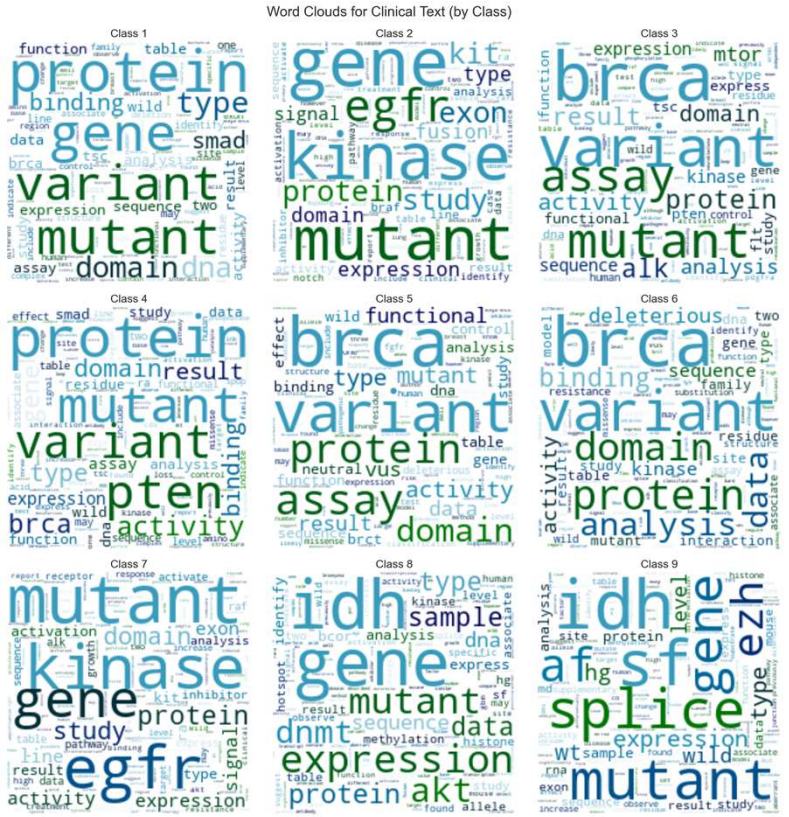
Case conversion + Text extraction

an unselected series of colorectal carcinomas stratified according to microsatellite instability msi and dna ploidy was examined for mutations and or promoter hypermethylation of five components of the wnt signaling cascade apc ctnnb encoding catenin axin tcf and wisp and three genes indirectly affecting this pathway cdh encoding e cadherin pten and tp apc and tp mutations were each present more often in microsatellite stable mss tumors

Tokenisation + Part-of-speech (POS) tagging + Lemmatisation + Stop-word removal

~5 hrs for training text
~1.5 hrs for test text

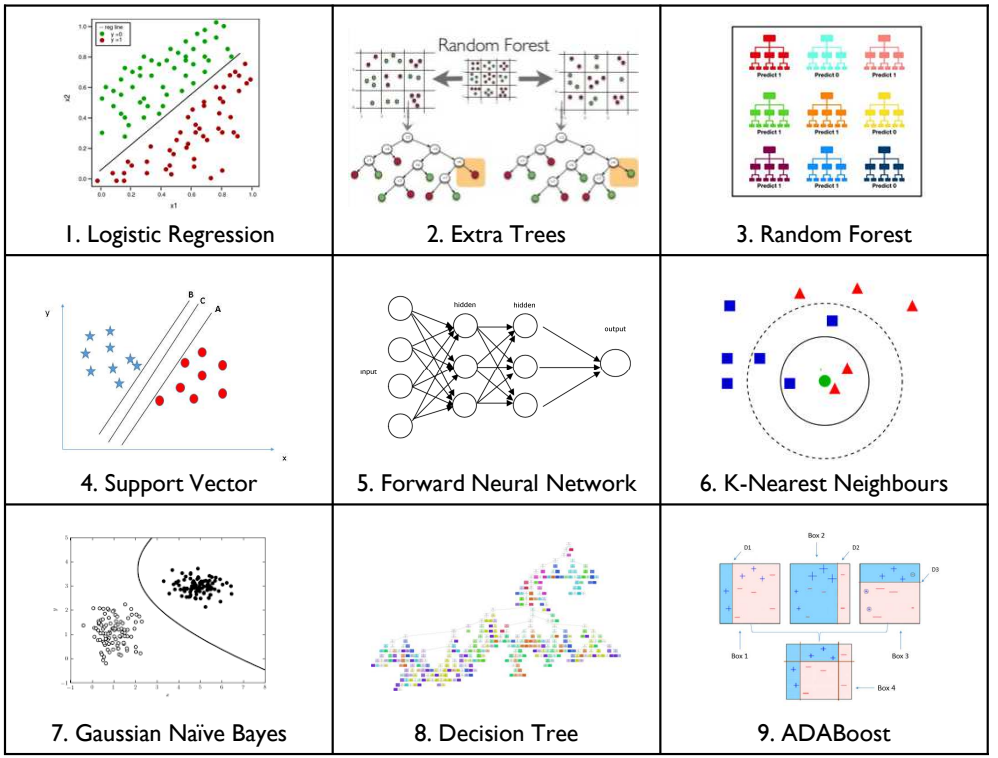
unselected series colorectal carcinoma stratify accord microsatellite instability msi dna ploidy examine promoter hypermethylation five component wnt signal cascade apc ctnnb encode catenin axin tcf wisp three gene indirectly affect pathway cdh encode e cadherin pten tp apc tp present often microsatellite stable ms

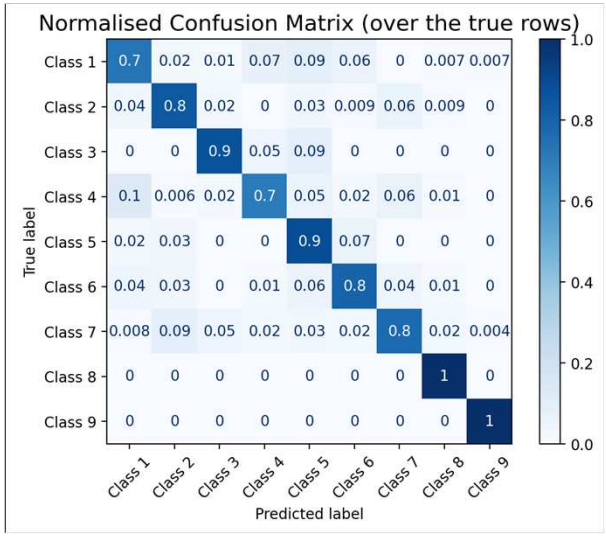


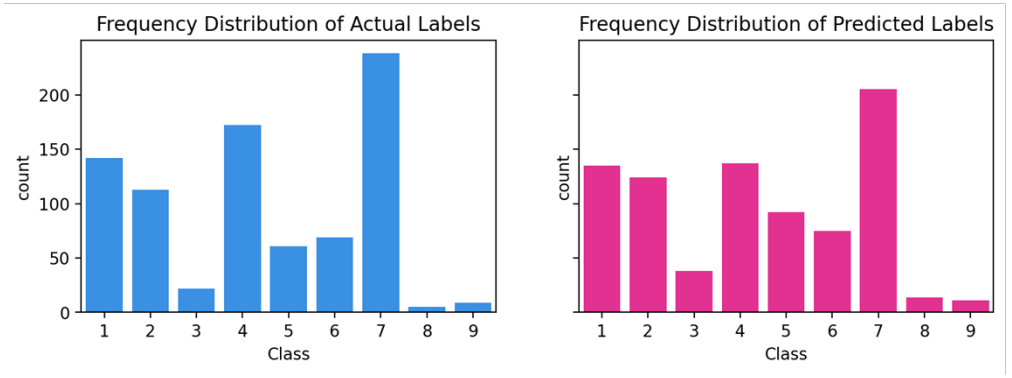
HOW WE BUILT OUR MODEL

- The key steps we took
  - We addressed our imbalanced classes – by creating more samples for selected classes (using ADASYN)
  - We made our model more generalisable – by 'pivoting' our data to reduce the number of features to just 1,800 (using PCA)
  - We systematically searched for the right model parameters – by identifying optimal parameters for 9 different candidates and ranking their performance
- We built a model consisting of a logistic regression classifier trained on weighted word counts

Best Performing Classifiers (1=Best)

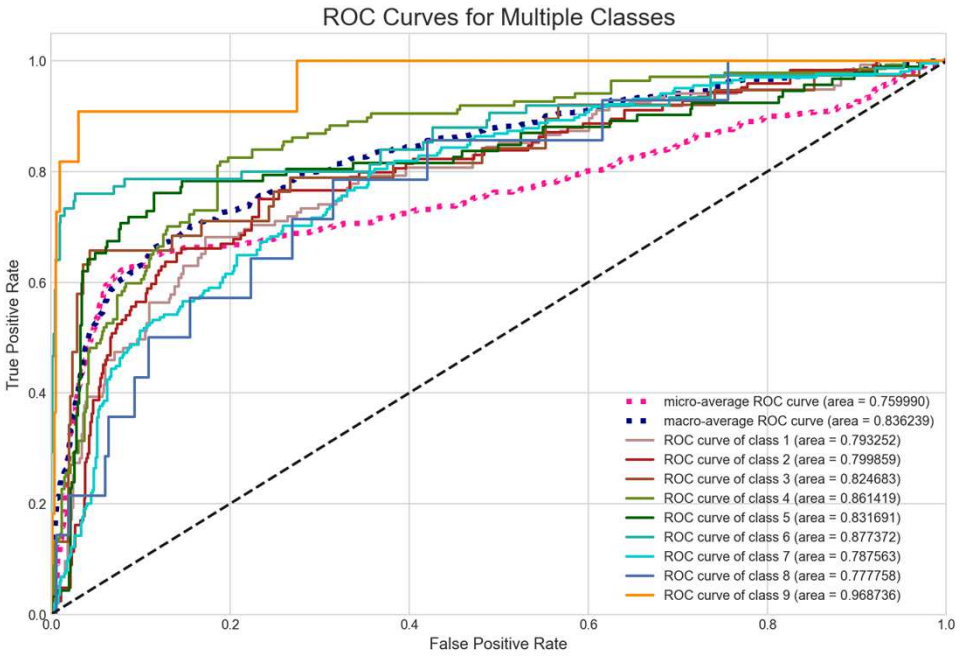






HOW DID OUR MODEL DO?

- Correctly predicts an average of ~54% of actual positives across all classes
- Has an average F1 score of ~62% for each class (weighted by the number of true instances of each class)
- Has an average AUC score of ~76% across all classes



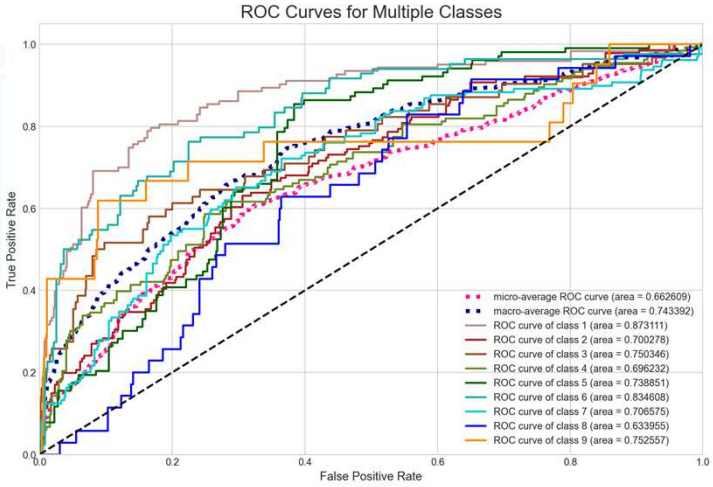
CAN WORD EMBEDDINGS IMPROVE OUR MODEL?

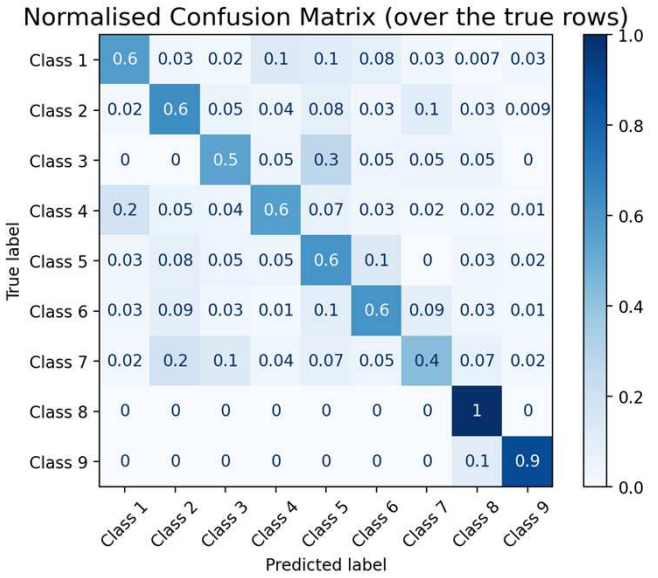
- The problem: we have too many features to begin with (~76k) because we are creating a feature for every unique word in all the training text
- The idea: use word embeddings which are representations of text in an n-dimensional space (100 dimensions in our case)
- The hope: we can train a model faster and achieve higher accuracy

unselected series colorectal carcinoma stratify accord microsatellite instability msi dna ploidy examine promoter hypermethylation five component wnt signal cascade apc ctnnb encode catenin axin tcf …

Text Instance	100-dimensional word embeddings					
	1	2	3	…	99	100
1	1.624678	-0.914357	-0.074222	…	0.997731	-0.449048
2	1.724697	-0.940365	-0.251819	…	1.002514	-0.585488
3	1.692799	-0.932071	-0.164691	…	0.950496	-0.45507
4	1.70435	-0.86725	-0.223373	…	1.00146	-0.539933
5	1.677125	-0.908731	-0.161353	…	0.99578	-0.496753
…	…	…	…	…	…	…

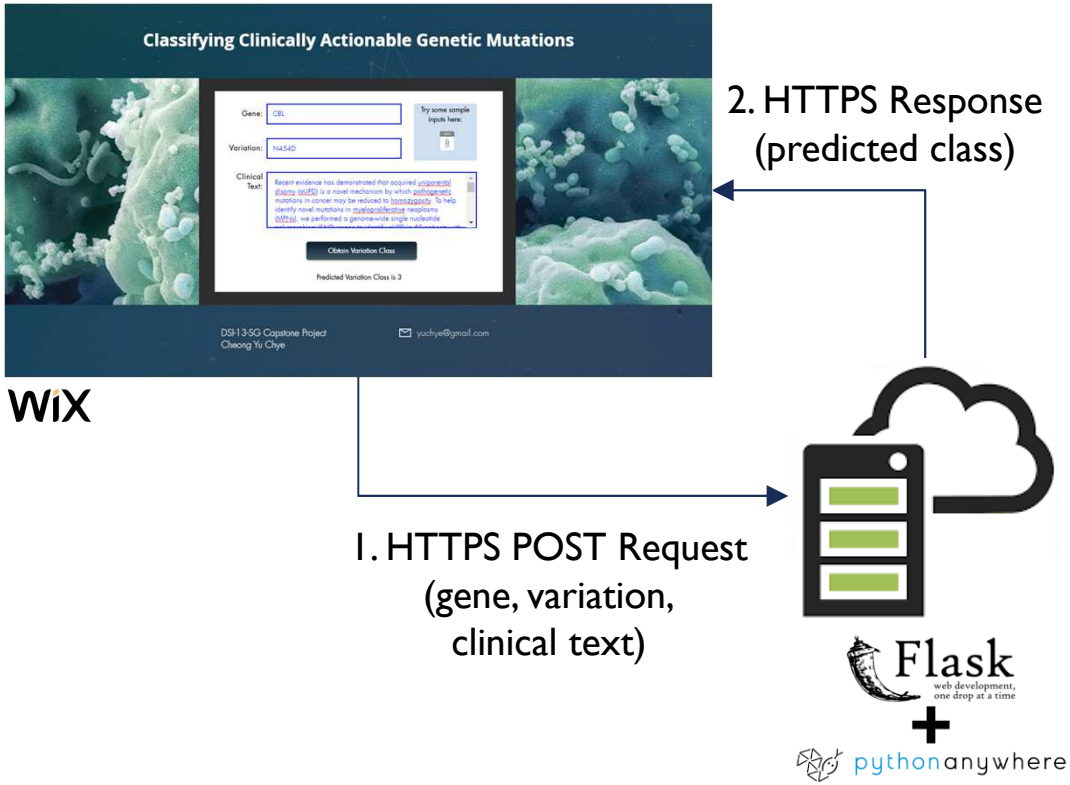
- The outcome: the best-trained alternative model had lower scores than our baseline model
- The conclusion: our baseline model is still a better choice





WEB DEPLOYMENT

- A web-based WIX front-end was built to facilitate real-time predictions (https://yuchye.wixsite.com/dsi-13-capstone)
  - Users can obtain the predicted variation class based on gene, variation and clinical text inputs
- The front-end builds a HTTPS POST request that is sent to a Flask web application that is hosted on a PythonAnywhere server
  - Our baseline model has been deployed as a stand-alone Python file which is executed on-the-fly

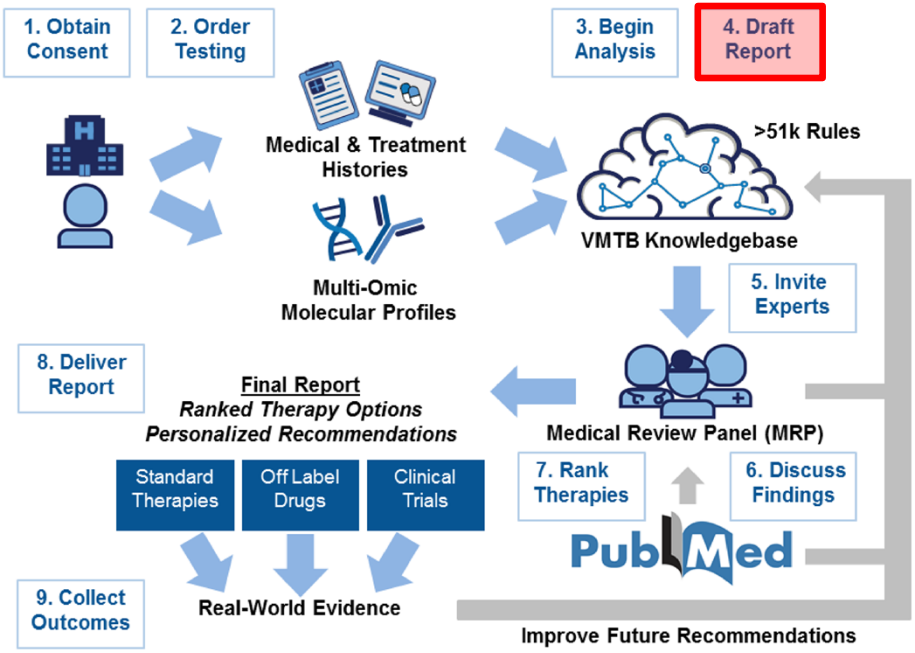


LIMITATIONS & RISKS

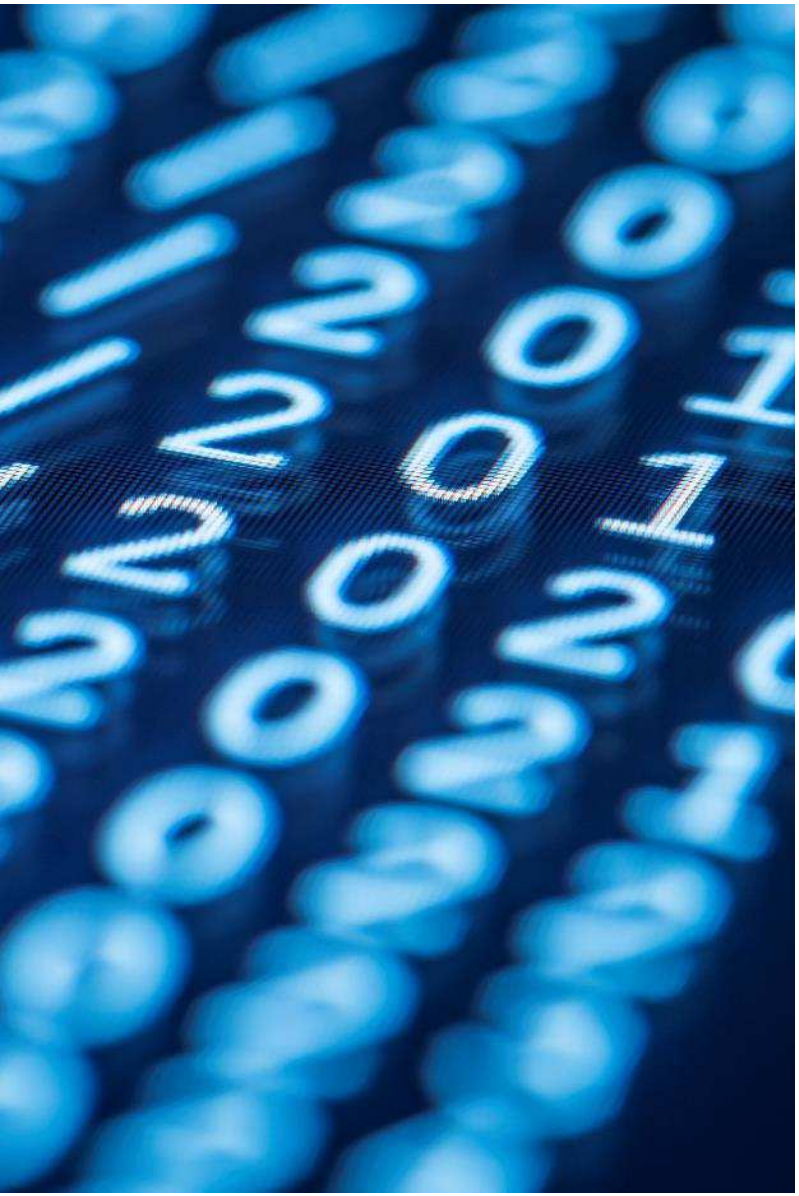
- Limitations
  - Character replacement approach – removal of potentially important characters
    - E.g. "E-cadherin" → "e cadherin", "β-catenin" → "catenin, "TP53" → "tp"
  - Subjective oversampling – a better approach may exist
  - Lack of biomedical context – significance or relatedness of keywords may not have been fully accounted for
  - Limited processing power and memory – we could not carry out a complete search for best classifier parameters
- Risk
  - Clinical pathologists' review is needed to validate the accuracy of our predictions

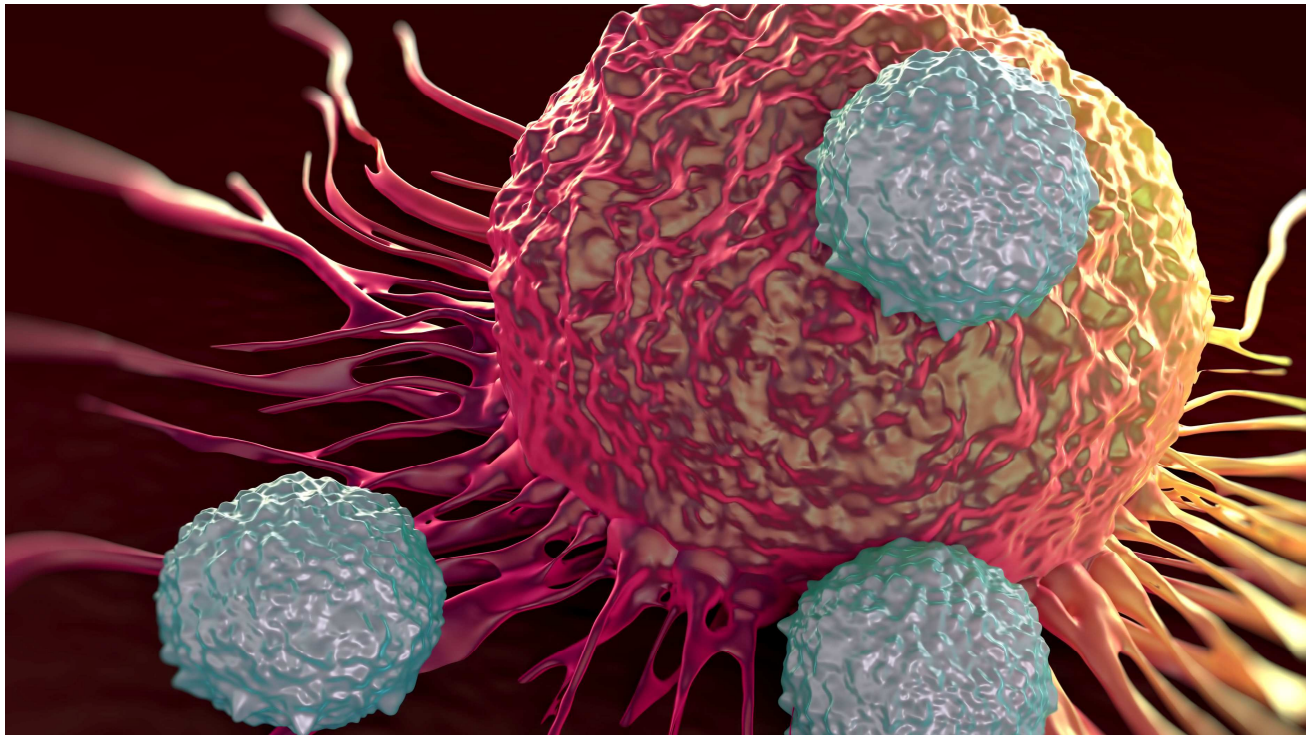
CONCLUSION

- We have successfully built a model that can help to automate the classification of biomedical literature relating to cancer mutations
- The model comprises a logistic regression classifier trained on weighted word counts
- Clinical pathologists can use the model to accelerate the classification process
- Our model predictions can be incorporated into reports that a medical review panel can use to make faster decisions on treatments or clinical trials that the patient could benefit from



Source: JAMIA Open, Volume 2, Issue 4, December 2019, Pages 505–515, https://doi.org/10.1093/jamiaopen/ooz045





THANK YOU

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