A Deep Learning System Classifies Cancer Origins Using Somatic Mutation Patterns Detected by Plasma Whole-Genome Sequencing

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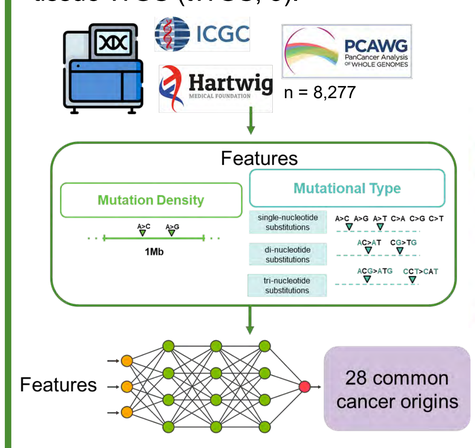
Introduction

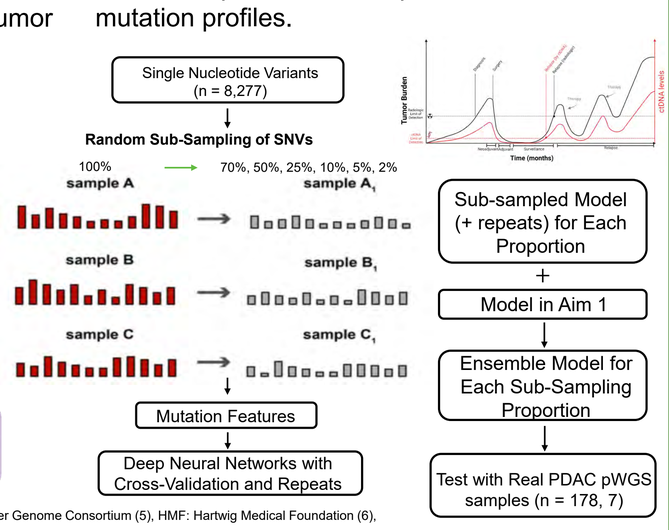
- A tumour's cell of origin is the single major predictor of the natural history of the disease (1).
- However, identifying the tumour's cell of origin can be complex, time-consuming, and error-prone in current clinical settings.
- Somatic passenger mutations capture the epigenetic state of the cell of origin as different cell types have distinctive chromatin profiles (2).
- Tumour cells release circulating tumour DNA into the blood, containing somatic passenger mutations specific to the tumour's cell of origin.
- **Objective: To design a deep learning system to predict cancer origins utilizing passenger mutation profiles detected from circulating tumour DNA collected by plasma whole-genome sequence (pWGS) to aid cancer of unknown primary and early cancer identification.**

Methods

Aim 1. Create a deep learning model using somatic mutation profiles from tumor tissue WGS (tWGS; 3).

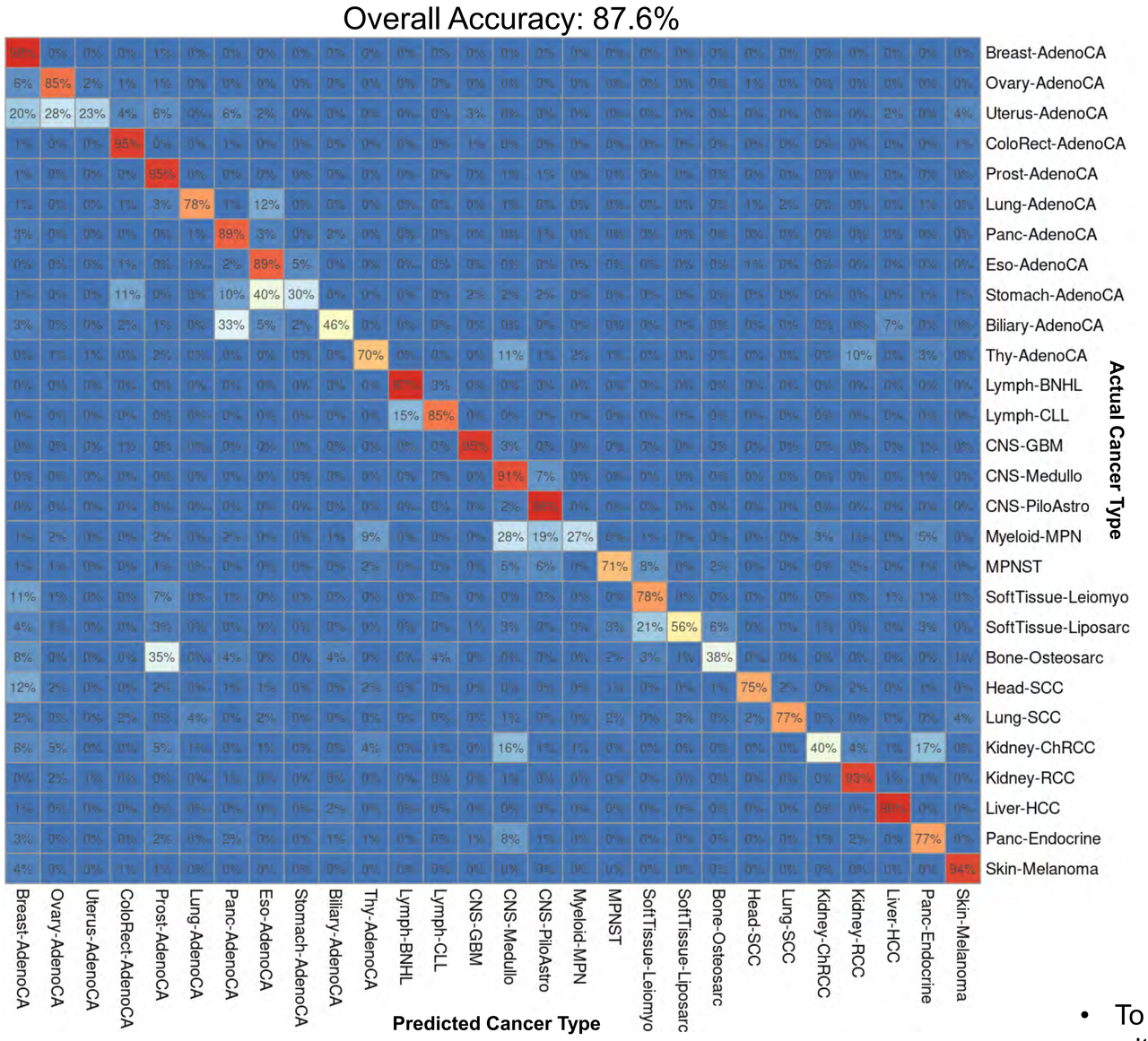


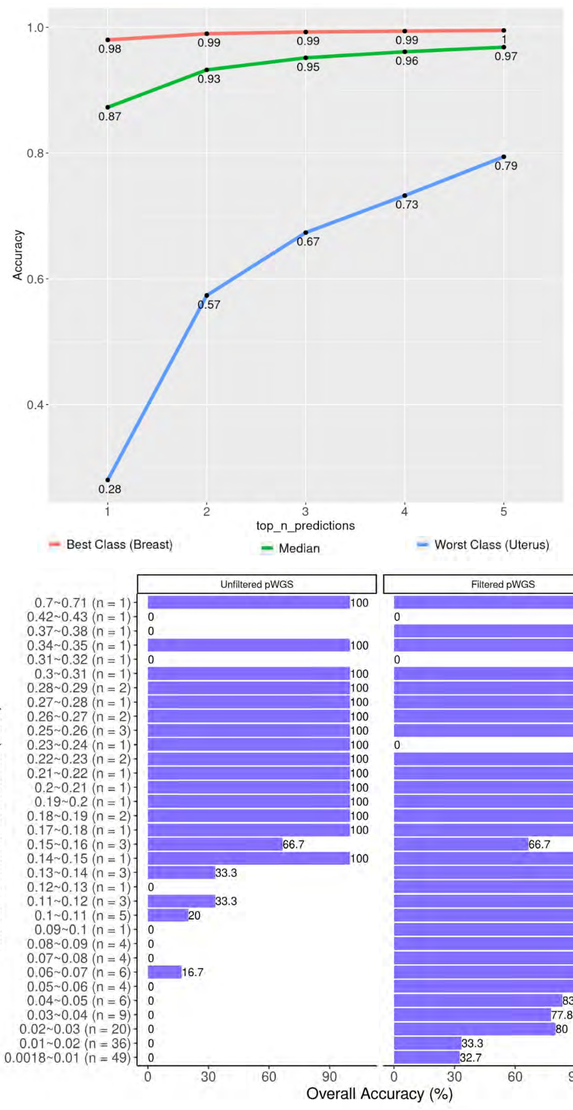
Aim 2. Adapt the model to pWGS somatic mutation profiles.

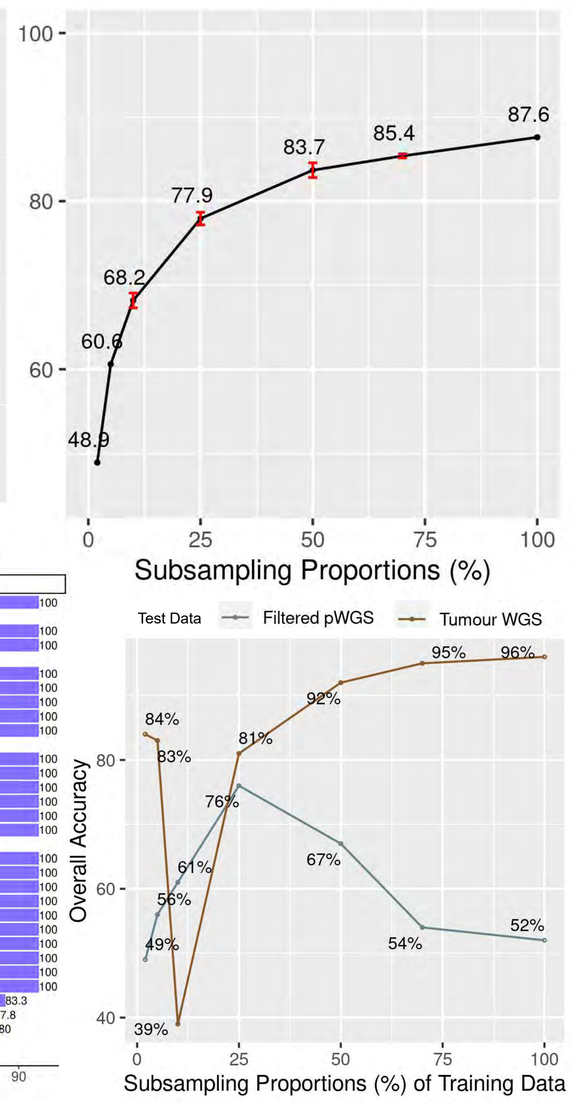


PCAWG: PanCancer Analysis of Whole Genome (4), ICGC: International Cancer Genome Consortium (5), HMF: Hartwig Medical Foundation (6), SNV: Single Nucleotide Variants, PDAC: Pancreatic Adenocarcinoma

Results







Aim 1. Create a deep learning model using somatic mutation profiles from tWGS:

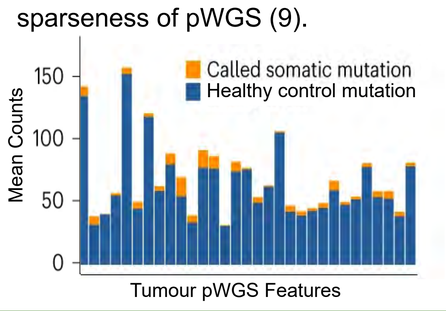
- We created a feed-forward neural network that predicted 28 common cancer types, with an overall held-out accuracy of 87.6%.
- Top N-rank analysis indicates that the model could be valuable for differential diagnosis.

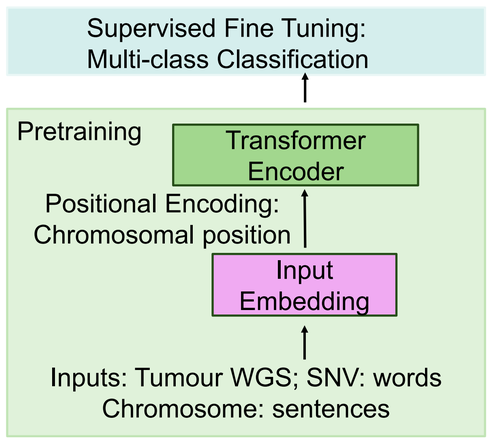
Aim 2. Adapt the model to pWGS somatic mutation profiles:

- The overall accuracy exceeded 78% when using more than 25% of the tWGS mutation profile of a patient.
- To validate the model in aim 1, classification accuracy in predicting PDAC (n = 178; 7) with tWGS was 96%. When using pWGS data from the same samples, filtered variants matched those found in tWGS (filtered pWGS), as the test data, we observed accuracies of 80-100% for samples with TRD ≥ 0.05. This indicates that the algorithm's performance is greatly improved when non-tumour variant calls are removed.
- Testing PDAC samples on our ensemble models showed that accuracies for tumour sample prediction were consistently above 80%, except for the model trained with 10% sub-sampling. For filtered pWGS samples, the highest classification accuracy was 76% with the model trained using 25% of each patient's tWGS mutation profile.

Future Proposal

- Estimate and remove non-tumour variant noise by subtracting variant profiles from a panel of normal controls (8).
- Use Bidirectional Encoder Representation Transformers to accommodate the sparseness of pWGS (9).





Conclusion

Our study presents the development of a feed-forward neural network trained with tWGS, capable of predicting 28 common cancer types with an overall accuracy of 87.6%. When training models with simulated pWGS somatic variant profiles by randomly sub-sampling a proportion of tWGS mutation profiles for each sample, the overall accuracy consistently surpassed 78% when using more than 25% of the mutation profiles. In the validation phase using real PDAC samples as the test data, the model achieved 96% accuracy with tWGS data, and the removal of non-tumour variants significantly improved accuracy in making prediction for pWGS data from the same samples. Our ensemble models, which combined the tWGS-trained model with models trained on simulated pWGS mutation profiles (and repeats), consistently exhibited accuracies above 80% for predicting PDAC tumour samples, except for the model trained with 10% of sub-sampling. Interestingly, using pWGS samples that excluded variants not matching those found in tWGS, as the test data, the highest classification accuracy was 76% with the model trained with 25% of each patient's tWGS mutation profile.

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