RNA sequencing-based Machine Learning for Detection of Triple Negative Breast Cancer

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**Abstract**

TNBC is an aggressive type of breast cancer that is difficult to treat and has a poor prognosis. It is most commonly diagnosed using immunohistochemistry (IHC), but this method is time-consuming and relies on an expert to interpret the result. The goal is to offer a simpler and more scalable diagnostic tool by building a machine learning model that can classify TNBC status using only RNA sequencing data.   
The proposed project will use the Breast Invasive Carcinoma Collection dataset from The Cancer Genome Atlas (TCGA-BRCA). The focus lies on a binary classification (TNBC versus non-TNBC), favouring simplicity over complexity, and prioritizing explainability, fairness and reproducibility of the model. The intention is to evaluate multiple machine learning algorithms and select the most effective one. The anticipated outcome is a transparent and accurate classification tool that makes use of explainable algorithms like Logistic Regression, Random Forest, and Support Vector Machines (SVM), which in turn provides an addition to current methods to show a TNBC diagnosis in research, to be applied when RNA sequencing data is available. All code, visualizations, and documentation will be made openly available to support reproducibility and future use.

**Keywords** Machine Learning · Triple Negative Breast Cancer · RNA sequence · Detection

**1 Introduction**

Breast cancer is one of the most common cancers in the world, and is a major cause of death for many people, in particular among (young) women [1] and people from low socio-economic backgrounds [2]. In 2022 female breast cancer was the second most common cancer with 2.3 million cases [3, 4]. As with all cancers, early and accurate diagnosis and classification are important for providing effective treatment. This project focuses on triple negative breast cancer (TNBC), one of the most aggressive, as TNBC proliferates more [5] and difficult to treat types of breast cancer due to lack of molecular targets [6]. About 15% of breast cancers are TNBC and these have a significantly worse prognosis than other types of breast cancer [7, 8].

A lack of expression of three hormone receptors defines TNBC: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [9].

Although neoadjuvant chemotherapy is the primary treatment modality for breast cancer in the early stage and used in conjunction with immunotherapy [10-12], TNBC does not respond to targeted hormone therapies due to the lack of related receptor markers [13], which limits treatment options and leads to a poorer prognosis for patients. Gene mutations and highly rearranged genomes characterize TNBC [14]. Initial therapeutic decisions are guided by PD-L1 expression and BRCA mutations [2].

The typing of TNBC done by Lehmann in 2011 [15], and cited recently [16-18], creating subtypes of TNBC, specifically basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal-like (MES), mesenchymal/stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR) [Fig. 1]. The subtypes have their own treatment modality. As ‘Lehmann typing’ is considered homogenous, recent TNBC typing is done using ‘Fudan typing’ [18-20] to indicate the subtypes. Another option for profiling for subtypes is ‘PAM50 intrinsic molecular sub­types’ [21]. For a recent extensive review on subtyping see the work of Asleh et al. [22].

Currently, diagnosis of TNBC can be performed using immunohistochemistry (IHC) to identify the presence or absence of ER, PR and HER2 from a tissue sample. Recently, liquid biopsy is emerging as a tool for diagnosing cancer [23]. Using IHC is considered the current clinical standard, although some contend there is no reliable biomarker [24].

IHC is time consuming, depends on a skilled operator, and not always available. Therefore, there is a need for additional diagnostic methods, especially in terms of speed, objectivity and reproducibility.In the past years, machine learning in particular has emerged as a powerful tool in research and diagnostics, especially in very large datasets such as with genomic data obtained from RNA sequencing given the accuracy and high sensitivity of RNA sequencing data [25]. Recent improvements in this area have shown a lot of promise for new possibilities of cancer classification. However, most research on this topic often focuses on TNBC subtypes or uses commercial tools that lack transparency, or uses large amounts of additional data that leads to complex models that lack explainability and might not be practical in all settings.

Although RNA sequencing provides a rich source of data for classification tasks, it also has its challenges, such as the high dimensionality of gene expression profiles, the biological heterogeneity among patients, and class imbalance in datasets, which leads to both practical and ethical concerns in its use.

Following ethical principles is essential, especially in a healthcare setting. As pointed out by Pinto et al., there is evidence for ethnicity specific determinants, and there exists a gap in genomic data between ethnicities [26]. The study of Asleh et al. showed the prevalence of the Chinese population in the LAR subtype [22]. Diagnostic tools based on machine learning must be transparent and understandable to be able to safely and ethically adopt them into practice, as well as to earn the trust of doctors [27, 28].

As such, there seems to be a gap in the creation of a simple, explainable and reproducible machine learning model that can classify TNBC status binary using RNA sequencing data alone. It is this gap that the project needs to fill.

This study proposes to build a binary classifier for TNBC status, trained on RNA sequencing data from The Cancer Genome Atlas (TCGA), more specifically the Breast Invasive Carcinoma Collection (TCGA-BRCA), given the detailed view the dataset offers [21, 29]. The goal is to explore if gene expression data by itself is sufficient to accurately identify TNBC status, and to do so in a way that emphasizes ethical principles such as transparency, reproducibility and algorithmic fairness.

**2 Literature Review**

Having reviewed existing open access literature on TNBC, whilst being aware of recent developments using multi-omics [25, 30, 31], this review has a focus on studies that use RNA sequencing and/or machine learning for diagnosis or classification.

Dass et al. [32] extensively reviewed current and potential future methods of diagnosing TNBC. Using IHC is the current clinical standard for diagnosis, despite its limitations [33], for identifying ER, PR and HER2 status which determines TNBC status. However, it is noted this method of diagnosis can be time consuming and relies on skilled operators.

One of the methods reviewed in Dass et al. was the *nCounter® Breast Cancer 360™ Panel* [34], a commercial tool that uses RNA expression levels from 770 genes to classify breast cancer. Although this tool looks promising in using RNA for classification, further research shows no mention of employing machine learning, and it being a commercial tool without any focus on explainability limits its usability for research purposes.

Further searching for TNBC and machine learning brought up Kothari et al. [35], who have also used the TCGA-BRCA dataset for TNBC classification. Their primary goal was identifying which genes are highly correlated with TNBC status and classification of subtypes, with a special focus on prognosis and survival. They have found 20 genes with strong potential but emphasized the need for further research. In addition to RNA sequencing data, they used methylation and miRNA data as well (leading to them using a smaller cohort from the TCGA-BRCA dataset due to limited availability of that data), but found this was not useful for predictions.

Looking more into TNBC vs. non-TNBC classification, Davis et al. [36] published a review of the genomic characteristics of TNBC cases, and noted that many subtypes of TNBC are very close to subtypes of non-TNBC, showing that classification is complex and that there is a lot of overlap on the gene level between TNBC and non-TNBC. Their review focuses on the implications of this for the development of targeted therapies for different subtypes of TNBC, but does not mention machine learning.

Finally, the research of molecular classification of TNBC is heterogeneous and challenging to treat [21, 37]. To explore treatment modalities, it is suggested to have subtypes of TNBC. Literature shows multiple subtyping classifications; PAM50, Lehmann, Burstein, Jézéquel, FUSCC [2, 22]. However, their focus was on classifying cases that were already known to be TNBC into subtypes, rather than the classification of TNBC versus non-TNBC.

From this literature review, it becomes apparent that RNA sequencing and machine learning have been used in the classification of TNBC and breast cancer in general, but there remains a gap in the development of a simple, transparent and reproducible classification model that focuses only on identifying TNBC status (yes or no) using RNA sequencing data alone. Previous studies have often focused on subtype classification, relied on additional data that might not have been predictive, or referred to commercial tools that lack transparency. To address this gap, this study proposes as a solution the training of a machine learning model using publicly available RNA sequencing data.

This

**3 Methods and Material**

**3.1 Overall Description of the Proposed Model**

Making use of available literature, the approach used in this study is based on proven approaches [38]. A visual representation is shown in Fig 1.

The elementary event that will be used as a classifier is TNBC status. The two possible values are True (TNBC) and False (~TNBC), which allow two complementary and disjoint equivalence classes [39].

Technology used is Python 3.12.7, Jupyter Notebook 7.2.2, both are packaged by Anaconda version 2.6.6.

Clinical data is filtered for TNBC status and used to get the RNA sequence data. Missing data and imbalance is addressed. Data is normalized using <xyz>. The featureset is split into a testset and validationset with a ratio of 8:2. Correlation is applied, and LASSO is used to do something extra.

Models used are SVM, Random Forest and Logistic Regression. <further substantiate the why>.

Lastly, analysis is applied.

**3.2 Datasets**

This study uses the TCGA-BRCA on the GDC portal. The number of cases [n] is 1098. The clinical data and the RNA sequence is used.

First the clinical data is loaded, which has 113 dimensions. Cases that have missing values is discarded. Determining the TNBC status based on the dimensions ‘er\_status\_by\_ihc', 'pr\_status\_by\_ihc' and 'her2\_status\_by\_ihc’ shows 116 cases having TNBC and 863 cases not having TNBC.

**3.3 Data PreProcessing**

Attention to missing values and imbalance in the dataset has a focus in preprocessing.

To bring balance in the dataset we apply Synthetic Minority Oversampling Technique (SMOTE) [40, 41]. The SMOTE algorithm creates a better balance by synthesizing new samples from the minority class.

**3.4 Feature Selection**

Multiple approaches are used for feature selection. Using the list of twenty proteins suggested by Kohari et al is one approach [35]. Another approach is based on assessing 65 open access research papers for insights into possible, relevant, biomarkers and oncogenes that are related to TNBC. For example, very recent research suggests the LRPPRC gene as a distinct marker for TNBC [42]. Following practices in machine learning studies, this study uses the Boruta package as another way to select features [38, 43, 44].

See table 1 for the resulting selected features.

Data integration nvt, multiomics

**A diagram of a process flow

AI-generated content may be incorrect.**

Fig 1 uit source [38] AANPASSEN!

Some general info on the FeatureSets on 18th May:

FeatureSet1 = the three markers that determine if BC is TNBC

FeatureSet2 = the result of reviewing 65 papers, based on human selection, selecting the markers that the papers said is a biomarker, close to a biomarker, or considered an oncogene.

FeatureSet3 = all genes with more than 1 reference, thus excluding a recently found biomarker LRPPRCC [42].

FeatureSet4 = all genes. This does not adhere to the rule “n/p > 5”, as n = 997 and p = 290.

The heuristic measure of “n/p > 5” is applied to feature selection [30].

**3.5 Data Integration**

Asfdsfsfsfs

**3.6 Classification and Prediction Modelling**

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**3.7 Implementation**

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**3.8 Evaluation**

To generate metrics, Python and Matplotlib were used. Specifically, the ROC curve, AUC, accuracy, sensitivity, and F1 served as indicators for evaluation of the model.

In order to understand the models LIME and SHAP are used [30]. Both these algorithms can make the output of models more explainable.

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**4 Results and Discussion**

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**5 Conclusions**

In conclusion, the model developed using RNA sequencing data demonstrates <xyz>.

**5.1 Innovations**

Oftewel, hier komt ‘what can be researched next’

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