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**

In assessing the current research on TNBC this study frames the developments for treatment of TNBC into four main areas. A point of note in the approach for literature review is that only open access literature has been reviewed. Below, each area is summarized, after which this study is positioned within the framework developed.

**Tumor microenvironment (TME) / tumor immune microenvironment (TIME)**

Comprehensive understanding of the TME is the basis for immunotherapy [30]. A key role of TME is the genesis, development, and metastasis of cancer. Within the TME different types of (non-cancerous) cells, including immune, endothelial, and adipocytes cells, continuously interact with cancer cells, thereby having a pronounced effect on growth and progression of a tumor [31, 32]. Regarding progression, and treatment, the TIME plays an increasing role although the understanding of the processes is incomplete [14]. Within the context of subtypes, the TIME has also been included in recent research [33].

**Subtyping**

Within different subtypes of TNBC the heterogeneity of TME is notably pronounced [32, 33]. Initial therapeutic decisions are based on a limited set of biomarkers (PD-L1, gBRCA, ki-67). As TNBC is heterogeneous, to improve diagnosis and treatment there are multiple classifications of subtypes. Classifications like PAM50, Lehmann, Burstein, Jézéquel, and Fudan University Shanghai Cancer Center (FUSCC). Where Lehmann and Burstein have similarities, Jézéquel puts emphasis on immune-relative factors, and FUSCC is recognized as a system tailored specifically for Chinese patients [2]. As for subtyping and ethnicity, there is a gap in genomic information between ethnicities, especially regarding the African continent where a higher TNBC incidence is observed, and the continent has the highest genomic diversity [26]. In addition to the aforementioned classifications, other subtyping has been suggested based on metabolics [34]. Recent developments in different approaches in determining subtypes are differential sparse canonical correlation analysis network (DSCCN) [35] and Multi-Omics Adaptive Integration Method with Graph Learning and Self Attention (MoAGL-SA) [29]. The heterogeneity of TNBC as revealed by transcriptomic and proteomics underlines the importance of a multi-omics approach [22].

**Multi-omics**

By applying the technology of multi-omics, enabling simultaneous analysis of different layers, both the broadening of the scope, and understanding of, the heterogeneity is facilitated. Use of multi-omics include mapping intra-tissue interactions, DNA mutations, protein expression levels, epigenetic modifications, and intercellular communications [36]. The variability of the omics data also plays a role in benchmarking studies [37], although the use of multi-omics comes with challenges like integration of data [38]. Spatial omics can dissect further differences of cells in tissue [39]. Different types of spatial omics have been developed and can be defined into two categories. On the one hand deciphering characterizations of regions (spacecraft-like) and outlining the structure of the tumor (telescope-like). An example of spacecraft-like is Laser Capture Microdissection (LCM) which discovered a novel biomarker [40].

**Biomarkers and prognosis**

While the main treatment modality remains chemotherapy, the in-depth research into the molecular heterogeneity of TNBC provides new perspectives for other forms of therapy like immune modulators [13]. Trying to find targets for treatment in, for example, differential expressed genes (DEGs) [41], extracellular vesicles (EVs) derived from plasma [23], or Oxidative phosphorylation (OXPHOS) [42].

**Current study**

Given the complexity of the TME environment and the multi-omics approach, this study tries to reduce complexity and aims to create a classification model that identifies TNBC status based on (predictive) biomarkers using RNA sequencing data. Given the background portrayed through this literature review, this study follows by setting out the methods, results, discussion and conclusion.

**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 [43]. 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 [44].

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) [45, 46]. 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 [47]. 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 [43, 48, 49].

See table 1 for the resulting selected features.

Data integration nvt, multiomics

**A diagram of a process flow

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Fig 1 uit source [43] 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 [38].

**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 [38]. 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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# References

[1] S. Zhu *et al.*, "Recent advances in targeted strategies for triple-negative breast cancer," *Journal of Hematology & Oncology,* vol. 16, no. 1, p. 1d, 2023/08/28 2023, doi: 10.1186/s13045-023-01497-3.

[2] Z. Chen *et al.*, "Classifications of triple-negative breast cancer: insights and current therapeutic approaches," *Cell & Bioscience,* vol. 15, no. 1, p. 13, 2025/02/01 2025, doi: 10.1186/s13578-025-01359-0.

[3] W. H. Organization. "Global cancer burden growing, amidst mounting need for services." <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services> (accessed 05/10/2025, 2025).

[4] H. Sung *et al.*, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," (in eng), *CA Cancer J Clin,* vol. 71, no. 3, pp. 209-249, May 2021, doi: 10.3322/caac.21660.

[5] J. C. Martin *et al.*, "Aryl hydrocarbon receptor suppresses STING-mediated type I IFN expression in triple-negative breast cancer," *Scientific Reports,* vol. 14, no. 1, p. 5731, 2024/03/08 2024, doi: 10.1038/s41598-024-54732-3.

[6] R. S. Bouzid *et al.*, "Molecular subtyping and target identification in triple negative breast cancer through immunohistochemistry biomarkers," *BMC Cancer,* vol. 25, no. 1, p. 2, 2025/03/13 2025, doi: 10.1186/s12885-025-13832-7.

[7] A. C. Association. "Triple-negative Breast Cancer." <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html> (accessed 05/10/2025, 2025).

[8] Q. Xue *et al.*, "LRPPRC confers enhanced oxidative phosphorylation metabolism in triple-negative breast cancer and represents a therapeutic target," *Journal of Translational Medicine,* vol. 23, no. 1, p. 2, 2025/03/25 2025, doi: 10.1186/s12967-024-05946-6.

[9] M. Matossian, N. Chen, and R. Nanda, "Exploiting Therapeutic Vulnerabilities in Triple-Negative Breast Cancer: Successes, Challenges, and Opportunities," *Current Breast Cancer Reports,* vol. 15, no. 3, p. 1, 2023/09/01 2023, doi: 10.1007/s12609-023-00492-4.

[10] X. Xiong, X. Wang, C.-C. Liu, Z.-M. Shao, and K.-D. Yu, "Deciphering breast cancer dynamics: insights from single-cell and spatial profiling in the multi-omics era," *Biomarker Research,* vol. 12, no. 1, p. 107, 2024/09/18 2024, doi: 10.1186/s40364-024-00654-1.

[11] B. Zhu *et al.*, "Injectable supramolecular hydrogel co-loading abemaciclib/NLG919 for neoadjuvant immunotherapy of triple-negative breast cancer," *Nature Communications,* vol. 16, no. 1, p. 687, 2025/01/15 2025, doi: 10.1038/s41467-025-55904-z.

[12] H. Bischoff, M. Espié, and T. Petit, "Neoadjuvant Therapy: Current Landscape and Future Horizons for ER-Positive/HER2-Negative and Triple-Negative Early Breast Cancer," *Current Treatment Options in Oncology,* vol. 25, no. 9, pp. 1210-1224, 2024/09/01 2024, doi: 10.1007/s11864-024-01251-y.

[13] W. Ren *et al.*, "Comprehensive analysis of metabolism-related gene biomarkers reveals their impact on the diagnosis and prognosis of triple-negative breast cancer," *BMC Cancer,* vol. 25, no. 1, p. 668, 2025/04/11 2025, doi: 10.1186/s12885-025-14053-8.

[14] S. Roostee *et al.*, "Tumour immune characterisation of primary triple-negative breast cancer using automated image quantification of immunohistochemistry-stained immune cells," *Scientific Reports,* vol. 14, no. 1, p. 21417, 2024/09/13 2024, doi: 10.1038/s41598-024-72306-1.

[15] B. D. Lehmann *et al.*, "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies," *The Journal of clinical investigation,* vol. 121, no. 7, pp. 2750-2767, 2011.

[16] S. Zhu *et al.*, "Recent advances in targeted strategies for triple-negative breast cancer," *Journal of Hematology & Oncology,* vol. 16, no. 1, p. 2, 2023/08/28 2023, doi: 10.1186/s13045-023-01497-3.

[17] Y. Li *et al.*, "Recent advances in therapeutic strategies for triple-negative breast cancer," *Journal of Hematology & Oncology,* vol. 15, no. 1, p. 2, 2022/08/29 2022, doi: 10.1186/s13045-022-01341-0.

[18] R. S. Bouzid *et al.*, "Molecular subtyping and target identification in triple negative breast cancer through immunohistochemistry biomarkers," *BMC Cancer,* vol. 25, no. 1, pp. 1-16, 2025/03/13 2025, doi: 10.1186/s12885-025-13832-7.

[19] Y. Z. Jiang *et al.*, "Genomic and Transcriptomic Landscape of Triple-Negative Breast Cancers: Subtypes and Treatment Strategies," (in eng), *Cancer Cell,* vol. 35, no. 3, pp. 428-440.e5, Mar 18 2019, doi: 10.1016/j.ccell.2019.02.001.

[20] Y. R. Liu *et al.*, "Comprehensive transcriptome analysis identifies novel molecular subtypes and subtype-specific RNAs of triple-negative breast cancer," (in eng), *Breast Cancer Res,* vol. 18, no. 1, p. 33, Mar 15 2016, doi: 10.1186/s13058-016-0690-8.

[21] M. M. O. Ortiz and E. R. Andrechek, "Molecular Characterization and Landscape of Breast cancer Models from a multi-omics Perspective," *Journal of Mammary Gland Biology and Neoplasia,* vol. 28, no. 1, pp. 1-13, 2023/06/03 2023, doi: 10.1007/s10911-023-09540-2.

[22] K. Asleh, N. Riaz, and T. O. Nielsen, "Heterogeneity of triple negative breast cancer: Current advances in subtyping and treatment implications," *Journal of Experimental & Clinical Cancer Research,* vol. 41, no. 1, pp. 1-26, 2022/09/01 2022, doi: 10.1186/s13046-022-02476-1.

[23] G. H. Tamarindo *et al.*, "Distinct proteomic profiles of plasma-derived extracellular vesicles in healthy, benign, and triple-negative breast cancer: candidate biomarkers for liquid biopsy," *Scientific Reports,* vol. 15, no. 1, p. 12122, 2025/04/09 2025, doi: 10.1038/s41598-025-95232-2.

[24] Q. Xue *et al.*, "LRPPRC confers enhanced oxidative phosphorylation metabolism in triple-negative breast cancer and represents a therapeutic target," *Journal of Translational Medicine,* vol. 23, no. 1, p. 11, 2025/03/25 2025, doi: 10.1186/s12967-024-05946-6.

[25] P. Tan *et al.*, "Application of omics technologies in studies on antitumor effects of Traditional Chinese Medicine," *Chinese Medicine,* vol. 19, no. 1, pp. 1-20, 2024/09/09 2024, doi: 10.1186/s13020-024-00995-x.

[26] R. J. Pinto *et al.*, "Coding and regulatory somatic profiling of triple-negative breast cancer in Sub-Saharan African patients," *Scientific Reports,* vol. 15, no. 1, p. 10325, 2025/03/25 2025, doi: 10.1038/s41598-025-94707-6.

[27] T. Vidalis, "Artificial Intelligence in Biomedicine: A Legal Insight," *BioTech*, vol. 10, no. 3*,* doi: 10.3390/biotech10030015.

[28] B. C. Stahl, D. Schroeder, and R. Rodrigues, "Right to Life, Liberty and Security of Persons," in *Ethics of Artificial Intelligence: Case Studies and Options for Addressing Ethical Challenges*, B. C. Stahl, D. Schroeder, and R. Rodrigues Eds. Cham: Springer International Publishing, 2023, pp. 63-78.

[29] L. Cheng *et al.*, "MoAGL-SA: a multi-omics adaptive integration method with graph learning and self attention for cancer subtype classification," *BMC Bioinformatics,* vol. 25, no. 1, p. 364, 2024/11/23 2024, doi: 10.1186/s12859-024-05989-y.

[30] Z. Guo *et al.*, "Tumor microenvironment and immunotherapy for triple-negative breast cancer," *Biomarker Research,* vol. 12, no. 1, p. 166, 2024/12/31 2024, doi: 10.1186/s40364-024-00714-6.

[31] J. Wu, J. Li, H. Xu, N. Qiu, X. Huang, and H. Li, "Periostin drives extracellular matrix degradation, stemness, and chemoresistance by activating the MAPK/ERK signaling pathway in triple–negative breast cancer cells," *Lipids in Health and Disease,* vol. 22, no. 1, pp. 1-14, 2023/09/16 2023, doi: 10.1186/s12944-023-01912-1.

[32] Y. Liu *et al.*, "Advances in immunotherapy for triple-negative breast cancer," (in eng), *Mol Cancer,* vol. 22, no. 1, p. 145, Sep 2 2023, doi: 10.1186/s12943-023-01850-7.

[33] M. Aine *et al.*, "The DNA methylation landscape of primary triple-negative breast cancer," *Nature Communications,* vol. 16, no. 1, p. 3041, 2025/03/28 2025, doi: 10.1038/s41467-025-58158-x.

[34] L. Weng, J. Zhou, S. Guo, N. Xu, and R. Ma, "The molecular subtyping and precision medicine in triple-negative breast cancer---based on Fudan TNBC classification," *Cancer Cell International,* vol. 24, no. 1, p. 120, 2024/03/30 2024, doi: 10.1186/s12935-024-03261-0.

[35] Y. Huang, P. Zeng, and C. Zhong, "Classifying breast cancer subtypes on multi-omics data via sparse canonical correlation analysis and deep learning," *BMC Bioinformatics,* vol. 25, no. 1, pp. 1-19, 2024/03/27 2024, doi: 10.1186/s12859-024-05749-y.

[36] X. Liu *et al.*, "Spatial multi-omics: deciphering technological landscape of integration of multi-omics and its applications," *Journal of Hematology & Oncology,* vol. 17, no. 1, pp. 1-24, 2024/08/24 2024, doi: 10.1186/s13045-024-01596-9.

[37] E. Brombacher, O. Schilling, and C. Kreutz, "Characterizing the omics landscape based on 10,000+ datasets," *Scientific Reports,* vol. 15, no. 1, p. 3189, 2025/01/25 2025, doi: 10.1038/s41598-025-87256-5.

[38] A. Morabito, G. De Simone, R. Pastorelli, L. Brunelli, and M. Ferrario, "Algorithms and tools for data-driven omics integration to achieve multilayer biological insights: a narrative review," *Journal of Translational Medicine,* vol. 23, no. 1, pp. 1-26, 2025/04/10 2025, doi: 10.1186/s12967-025-06446-x.

[39] J. Qian *et al.*, "Identification and characterization of cell niches in tissue from spatial omics data at single-cell resolution," *Nature Communications,* vol. 16, no. 1, p. 1693, 2025/02/16 2025, doi: 10.1038/s41467-025-57029-9.

[40] S. Lee, G. Kim, J. Lee, A. C. Lee, and S. Kwon, "Mapping cancer biology in space: applications and perspectives on spatial omics for oncology," *Molecular Cancer,* vol. 23, no. 1, pp. 1-27, 2024/01/30 2024, doi: 10.1186/s12943-024-01941-z.

[41] W. Chen *et al.*, "Construction of the bromodomain-containing protein-associated prognostic model in triple-negative breast cancer," *Cancer Cell International,* vol. 25, no. 1, p. 18, 2025/01/18 2025, doi: 10.1186/s12935-025-03648-7.

[42] Q. Xue *et al.*, "LRPPRC confers enhanced oxidative phosphorylation metabolism in triple-negative breast cancer and represents a therapeutic target," *Journal of Translational Medicine,* vol. 23, no. 1, pp. 1-15, 2025/03/25 2025, doi: 10.1186/s12967-024-05946-6.

[43] A. M. Hassan, S. M. Naeem, M. A. A. Eldosoky, and M. S. Mabrouk, "Multi-omics-based Machine Learning for the Subtype Classification of Breast Cancer," *Arabian Journal for Science and Engineering,* vol. 50, no. 2, pp. 1339-1352, 2025/01/01 2025, doi: 10.1007/s13369-024-09341-7.

[44] J. J. Cuadrado-Gallego and Y. Demchenko, "Supervised Classification," in *Data Analytics: A Theoretical and Practical View from the EDISON Project*. Cham: Springer International Publishing, 2023, pp. 335-404.

[45] X. Song *et al.*, "Use of ultrasound imaging Omics in predicting molecular typing and assessing the risk of postoperative recurrence in breast cancer," *BMC Women's Health,* vol. 24, no. 1, p. 380, 2024/07/02 2024, doi: 10.1186/s12905-024-03231-8.

[46] G. Lemaître, F. Nogueira, and C. K. Aridas, "Imbalanced-learn: a python toolbox to tackle the curse of imbalanced datasets in machine learning," *J. Mach. Learn. Res.,* vol. 18, no. 1, pp. 559–563, 2017.

[47] C. Kothari *et al.*, "Machine learning analysis identifies genes differentiating triple negative breast cancers," *Scientific Reports,* vol. 10, no. 1, p. 10464, 2020, doi: 10.1038/s41598-020-67525-1.

[48] Y. Li, X. Wu, D. Fang, and Y. Luo, "Informing immunotherapy with multi-omics driven machine learning," *npj Digital Medicine,* vol. 7, no. 1, p. 67, 2024/03/14 2024, doi: 10.1038/s41746-024-01043-6.

[49] S. Li *et al.*, "Artificial intelligence learning landscape of triple-negative breast cancer uncovers new opportunities for enhancing outcomes and immunotherapy responses," *Journal of Big Data,* vol. 10, no. 1, p. 132, 2023/08/26 2023, doi: 10.1186/s40537-023-00809-1.