International Journal on Recent and Innovation Trends in Computing and Communication
ISSN: 2321-8169 Volume: 11 Issue: 10
DOI: https://doi.org/10.17762/ijritcc.v11i10.8465
***Article Received:** 23 July 2023 **Revised:** 16 September 2023 **Accepted:** 30 September 2023*

Yolov5 AI Deep Learning model driven Nuclear Pleomorphism Grading on Breast Cancer Pathology WSI for Nottingham Cancer Grading

AI Driven Nuclear Pleomorphism Grading on Breast Cancer Pathology WSI

Dr.Rajasekaran Subramanian[1], Dr.R.Devika Rubi[2], Dr.Rohit Tapadia[3], Dr.Archana Somani[4], Veera Venkata Rama Krishna Rao Ponugoti[5], Laxmi Kanth Reddy Kondam[6]

[1]PhD, Associate Professor, Dept. of Computer Science and Engineering
Keshav Memorial Institute of Technology
Hyderabad, India
e-mail: rajasekarans@kmit.in
[2]PhD, Associate Professor, Dept. of Computer Science and Engineering
Keshav Memorial Institute of Technology
Hyderabad, India
e-mail: devikarubir@kmit.in
[3]MD, Consultant – Pathology
Tapadia Diagnostics Center
Hyderabad, India
e-mail: rohittapadia@gmail.com
[4]MD, Associate Professor
Dr.Balasaheb Vikhe Patil Rural Medical College
Loni, Maharashtra
e-mail: archana.somani92@gmail.com
[5]Reserach Intern, Dept of Computer Science and Engineering
Keshav Memorial Institute of Technology
Hyderabad, India
e-mail: pvvramakrishnarao234@gmail.com
[6]Reserach Intern, Dept of Computer Science and Engineering
Keshav Memorial Institute of Technology
Hyderabad, India
e-mail: pvvramakrishnarao234@gmail.com

Abstract— Breast cancer is the second largest cancer caused in the world due to the uncontrollable growth in breast cells. Nottingham Grading is the internationally acceptable system to grade breast cancer. Nuclear pleomorphism is one of the breast cancer biomarkers for computing Nottingham grading. Pathologists grade nuclear pleomorphism on breast cancer glass tissue slides using a conventional microscope which is time consuming and has considerable inter-observer variability between pathologists. The paper proposed an Artificial Intelligence (AI) deep learning model to grade grade1, grade2, grade3 nuclear pleomorphism on breast cancer whole slide images (WSI). The proposed Yolov5 model is trained and tested on 1,30,000 WSI tiles having around two lakh annotations. The accuracy of the model is mAP 0.89. The proposed model saves the time and reduces the workload of the pathologist and also helps them to produce accurate results.

Keywords- Nuclear Pleomorphism grading, YoloV5, Breast Cancer WSI, Nottingham Cancer Grading, Digital Pathology.

I. INTRODUCTION

Breast cancer occurs due to the uncontrollable growth in breast cells which is the second largest cancer cause in the world. Cytology deviation [1] appears in breast cancer tissue. Histological Grading grades the tumour and its cytology deviation facilitates to decide on therapy. Conventional

International Journal on Recent and Innovation Trends in Computing and Communication
ISSN: 2321-8169 Volume: 11 Issue: 10
DOI: https://doi.org/10.17762/ijritcc.v11i10.8465
***Article Received:** 23 July 2023 **Revised:** 16 September 2023 **Accepted:** 30 September 2023*

Microscope is used by pathologists to perform histological grading which is time consuming and causes heavy workload to pathologists. Conventional Microscope grading produces inter observer variability between pathologists [2]. The invention of Digital Scanners and Deep Learning models reduces the above limitation and helps to improve the accuracy and the speed of histological grading. Digital Scanners digitise the class slide tissue into Whole Slide Images (WSI) [3]. They are in pyramid architecture and have various zoom levels with different numbers of tiles which are the smaller patches of WSI [4]. This architecture of WSI provides microscopic view to pathologists. Cytology deviation and tumour architecture in WSI are annotated by pathologists for training and development of deep learning models for histological grading. Nottingham Grading system [5] [6] grades breast cancer WSI using three bio markers namely mitotic count [7] [8], tubular formation [9] [10] and nuclear pleomorphism. Nuclear Pleomorphism [11] measures the morphological structure of cancer cells into three grades namely grade 1, grade 2 and grade 3. Nuclear Pleomorphism grade 1 cells are most like normal epithelial breast cells [12], Grade 3 cells are having greatest variation whereas grade 2 is very difficult to differentiate between grade 1 and grade 2. Grades of nuclear pleomorphism cells have poor inter observer agreement. Therefore, this paper proposes the YOLOv5 [13] model to grade three nuclear pleomorphism grades for breast cancer cells by using 1,30,000 WSI tiles of size 500 x 500 for 50 breast cancer patients with 40X magnification with overall mean average precision of 0.89.

II. RELATED WORKS

As nuclear pleomorphism scoring requires qualitative measurement, the existing literature faces difficulties to get proper annotated dataset to train Deep Learning Models. Caner Mercon et al. [14] proposed a continuous scoring deep learning approach in which instead of classifying three nuclear pleomorphism scoring, they applied continuous scoring for score 1 to score 3 by using deep regression network and they obtained 0.56 kappa correlation between the deep learning model and pathologists. Suzanne C et al. [15] [16] uses Multiple Instance Learning (MIL) model with ResNet-34 as backbone architecture to classify low, intermediate, and high-grade breast tumors. The model is pre-trained on ImageNet and trained by using the label of WSI which is a weak label dataset having top 5 probable tumor titles to represent a WSI. The model is trained by Job WSI and has a kappa correlation of 0.59 with F1 accuracy of 0.80.

Tissue Microarray (TMA) of 276 estrogen for breast cancer patients are used to study survival analysis and segment various nuclear pleomorphism scores of breast cancer by Cheng Lu et al. [17] They also discuss the higher correlation between ERT and nuclear pleomorphism that decides the adjuvant chemotherapy. They used the watershed algorithm to segment individual nuclei on 276 TMA spots and derived the features such as nuclear shape, texture and orientation disorder. They shared that there exists a greater nuclear variation for short term survival patients whereas uniform local nuclear variation occurred for long term survival patients. P. Maqlin et al. [18] developed deep belief neural networks (DBM - DMR) to classify the three grades of nuclear pleomorphism. They annotated 80 H&E tiles from the MITOS-ATYPIA dataset by three pathologists and provided the majority score of them as the label of the file. The framework has three major tasks such as detection of nuclei, feature extraction and classification of nuclei using DBN and achieved an accuracy of 90%.

Higher grade tumor reassures aggressive treatments due to its poor prognosis from the lower grade tumors Nottingham grade 2 patients are half those than Nottingham grade 1 and Nottingham grade 3. Y. Wang et al. [19] proposed a deep learning model called Deep Grade to classify Nottingham grade 1 and Nottingham grade 3 the extra layer to classify Nottingham grade 2. DeepGrade model is trained by three datasets ClinSeq, BC, TCGA-BC and SOSBC-1 with all 95%. Ronnachai Jaroensri et al. [20] discussed the strength of the AI based Nottingham grading system and developed a deep learning system for grading all the three components of NGS. DLS was trained by 1502 WSI and produced 0.50 quadratic kappa for nuclear pleomorphism scoring using the multivariable WX regression model.

III. PROPOSED WORK

A. Dataset Preprocessing

The proposed system collects 50 breast cancer patients WSI from the Indo-American and Tapadia diagnostics center, each WSI varies in size from 8 to 12 GB totaling approximately 132 GB. The WSI slides are digitized by Morphle Scanner [21] at 40X magnification and uploaded in cadd4mbc website. The WSI is stored as a pyramid structure of various zoom levels such as 5x,10x20x…40x,80x (extended digital zoom level). All levels contains same size of image called as tiles. The level zero contains lower resolution called as thumbnail. The number of tiles in further levels are increased with higher resolution. The lowest level contains maximum tiles with high resolution. The architecture of WSI is explained in fig.1

International Journal on Recent and Innovation Trends in Computing and Communication
ISSN: 2321-8169 Volume: 11 Issue: 10
DOI: https://doi.org/10.17762/ijritcc.v11i10.8465
Article Received: *23 July 2023* ***Revised:*** *16 September 2023* ***Accepted:*** *30 September 2023*

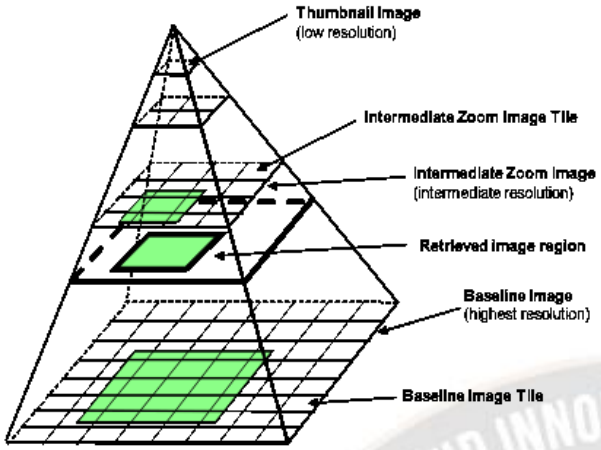

Fig. 1: Architecture of WSI

The digitized pyramid structure of WSI is shown in fig.2. It is a collection of folders for various zoom levels in which each level folder contains a list of images to represent the tiles in that respective level. The WSI architecture facilitates microscopic zoom in and zoom out effect to the pathologists.

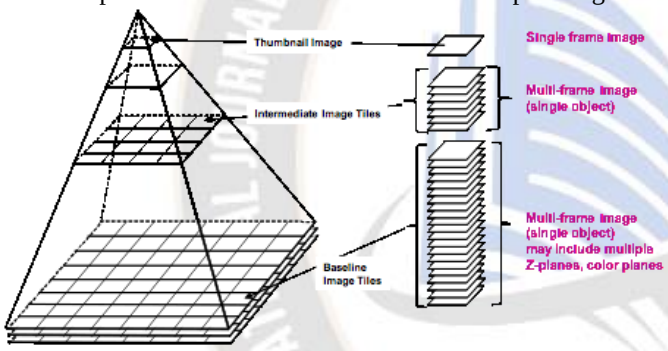

Fig 2: Digitized pyramid Structure of WSI

The uploaded WSI image is shown in Fig.3.

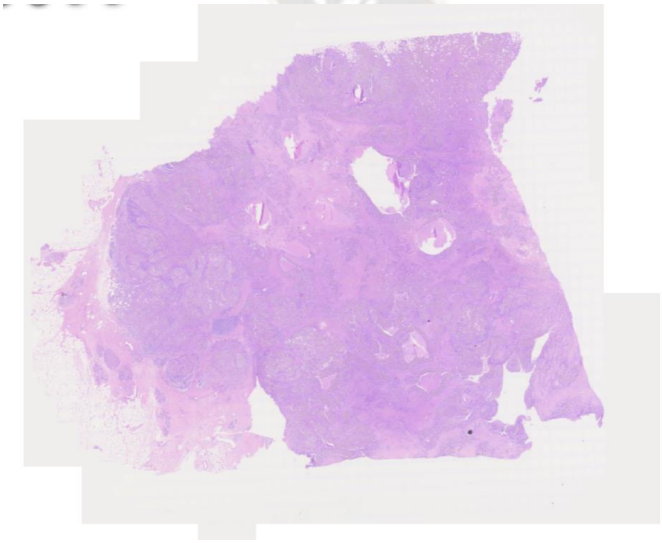

Fig.3: Uploaded WSI image

The uploaded images are divided into fields and the white tiles are removed. The files of size 500 x 500 are annotated by pathologist for Nuclear Pleomorphism grade 1, grade 2, grade 3 and bat files are created which have the format of bounding box (class, centre-x, centre-y, box-height, box-width). The annotated WSI image shown in Fig.4.

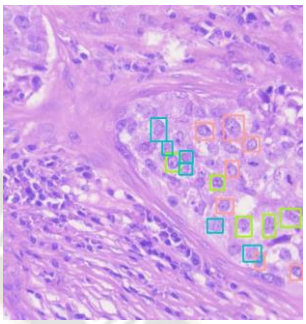

Fig.4: Annotated WSI Image file

The annotations on the images can be generated as JSON file, which is shown in Fig.5

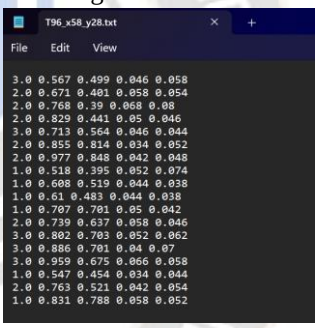

Fig.5: Generated JSON file of WSI annotations

After annotation vertical and horizontal flips are applied for data augmentation and the dataset is tripled. The complete dataset is described in Table 1.

Table 1: The sample dataset with annotation details

	Before Augmentation	After Augmentation
Annotations Grade 1	10,196	30,588
Annotations Grade 2	42,891	1,28,674
Annotations Grade 3	8,858	26,574

As the number of cells are not equally distributed for grade 1, grade 2, grade 3, to get accurate results, the proposed system performs training the deep learning model for all three grades together as well as the individual model training for each grade 1, grade 2 and grade 3.

International Journal on Recent and Innovation Trends in Computing and Communication
ISSN: 2321-8169 Volume: 11 Issue: 10
DOI: https://doi.org/10.17762/ijritcc.v11i10.8465
Article Received: *23 July 2023* ***Revised:*** *16 September 2023* ***Accepted:*** *30 September 2023*

B. Model Training and Results

The YOLOv5 model is trained to predict grade 1, grade 2 and grade 3 nuclear pleomorphism. The YOLOv5 model is different from the traditional multistage model due to its single stage prediction of objects by using bounding boxes. The sizes of bounding boxes are generated to predict objects with respect to the object sizes. The architecture of YOLOv5 contains three structures such as CSP Darknet53 as backbone, CSP PAN as neck and head to generate final output [13]. The backbone CSP Darknet extracts the features of the input image. The neck structure CSP PAN generates and scales up the pyramids for the features generated by the backbone. The head architecture creates bounding boxes for various sizes of the objects and achieves the optimal prediction.

The dataset described in table 1 is trained by YOLOv5. Each file is of size 500 x 500. The model is trained for 200 epochs with batch size 16. SGD is used as the optimizer and the learning rate is 0.01. The model is trained to obtain all three grades of nuclear pleomorphism such as grade 1, 2, 3. The model produces overall MAP as 0.79. The prediction for all three grades of nuclear pleomorphism is shown in fig. 6.

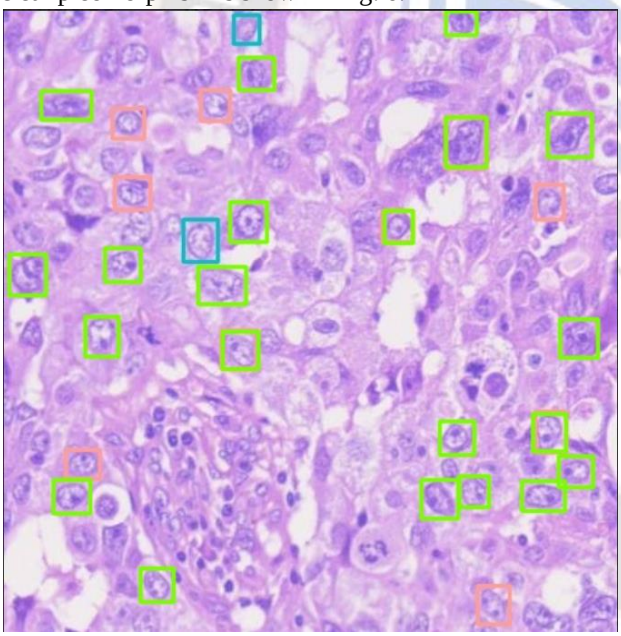

Fig.6. Nuclear predictions with three grades

As the combined dataset for all three grades are not equally distributed. Hence, the model is trained separately for individual grade 1, grade 2 and grade 3 dataset for 200 epochs with batch size 16. The individual models use SGD optimizer with 0.01 learning rate. The individual prediction is shown in fig.7.

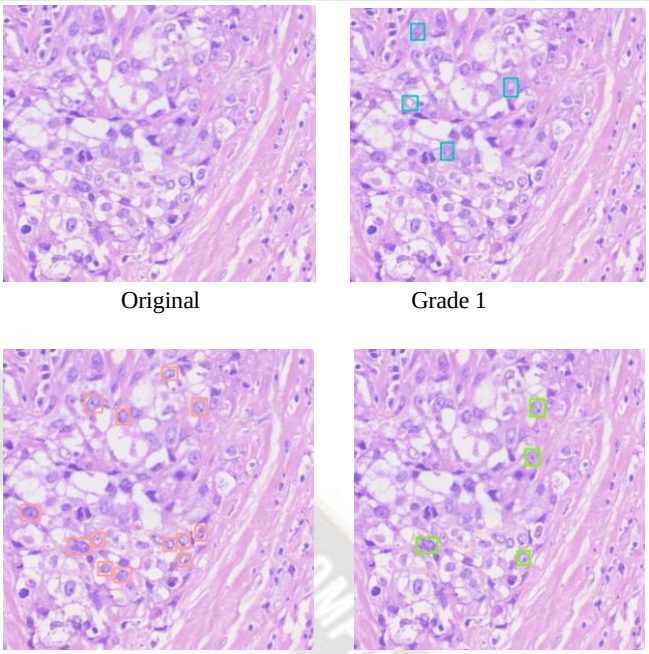

Fig.7: Individual Grade Predictions

The model produces 0.66, 0.85 and 0.53 as MAP for grade 1, grade 2 and grade 3 respectively. As grade 2 has a large amount of data around 1,30,000 produces a better MAP than grade 1 and grade 3 which have data size around 30,000 and 25,000 respectively. The model results can be further optimized by providing training on large annotated nuclear pleomorphism dataset.

IV. CONCLUSION AND THE FUTURE ENHANCEMENT

Nottingham grading is the universal acceptable grading for breast cancer. Nuclear pleomorphism is one of the scores needed for Nottingham grading to grade breast cancer. The proposed yolo v5 model is trained around 1,30,000 WSI tiles for grade1, grade2 and grade 3 individually as well as all three grades together and produces overall mAP as 0.89. The model needs further large annotation dataset to get further optimized results.

ACKNOWLEDGMENT

Prof. Neil Gogte, Director, Keshav Memorial Institute of Technology for the Project Guidance, Finance and Material support.

REFERENCES

[1] Mehrotra R, Yadav K. Breast cancer in India: Present scenario and the challenges ahead. World J Clin Oncol. 2022 Mar 24;13(3):209-218. doi: 10.5306/wjco.v13.i3.209. PMID: 35433294; PMCID: PMC8966510.

[2] 2 Ginter PS, Idress R, D'Alfonso TM, Fineberg S, Jaffer S, Sattar AK, Chagpar A, Wilson P, Harigopal M. Histologic grading of breast carcinoma: a multi-institution study of interobserver

International Journal on Recent and Innovation Trends in Computing and Communication
ISSN: 2321-8169 Volume: 11 Issue: 10
DOI: https://doi.org/10.17762/ijritcc.v11i10.8465
Article Received: *23 July 2023* ***Revised:*** *16 September 2023* ***Accepted:*** *30 September 2023*

variation using virtual microscopy. Mod Pathol. 2021 Apr;34(4):701-709. doi: 10.1038/s41379-020-00698-2. Epub 2020 Oct 19. PMID: 33077923; PMCID: PMC7987728.

[3] Pallua JD, Brunner A, Zelger B, Schirmer M, Haybaeck J. The future of pathology is digital. Pathol Res Pract. 2020 Sep;216(9):153040. doi: 10.1016/j.prp.2020.153040. Epub 2020 Jun 20. PMID: 32825928.

[4] Sui D, Liu W, Chen J, Zhao C, Ma X, Guo M, Tian Z. A Pyramid Architecture-Based Deep Learning Framework for Breast Cancer Detection. Biomed Res Int. 2021 Oct 1;2021:2567202. doi: 10.1155/2021/2567202. PMID: 34631877; PMCID: PMC8500767.

[5] BLOOM HJ, RICHARDSON WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer. 1957 Sep;11(3):359-77. doi: 10.1038/bjc.1957.43. PMID: 13499785; PMCID: PMC2073885.

[6] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991 Nov;19(5):403-10. doi: 10.1111/j.1365-2559.1991.tb00229.x. PMID: 1757079.

[7] Bochkovskiy, Alexey, Chien-Yao Wang, and Hong-Yuan Mark Liao. "Yolov4: Optimal speed and accuracy of object detection." arXiv preprint arXiv:2004.10934 (2020).

[8] Rajasekaran Subramanian, R. Devika Rubi, Rohit Tapadia, Katakam Karthik, Mohammad Faseeh Ahmed and Allam Manudeep, "Web based Mitosis Detection on Breast Cancer Whole Slide Images using Faster R-CNN and YOLOv5" International Journal of Advanced Computer Science and Applications(IJACSA), 13(12), 2022. http://dx.doi.org/10.14569/IJACSA.2022.0131268

[9] Rajasekaran Subramanian, R. Devika Rubi, Rohit Tapadia and Rochan Singh, "KMIT-Pathology: Digital Pathology AI Platform for Cancer Biomarkers Identification on Whole Slide Images" International Journal of Advanced Computer Science and Applications(IJACSA), 13(11), 2022. http://dx.doi.org/10.14569/IJACSA.2022.0131170

[10] Tekin, E., Yazıcı, Ç., Kusetogullari, H. et al. Tubule-U-Net: a novel dataset and deep learning-based tubule segmentation framework in whole slide images of breast cancer. Sci Rep 13, 128 (2023). https://doi.org/10.1038/s41598-022-27331-3

[11] Peregrina-Barreto H, Ramirez-Guatemala VY, Lopez-Armas GC, Cruz-Ramos JA. Characterization of Nuclear Pleomorphism and Tubules in Histopathological Images of Breast Cancer. Sensors (Basel). 2022 Jul 28;22(15):5649. doi: 10.3390/s22155649. PMID: 35957203; PMCID: PMC9371191.

[12] Brázdil T, Gallo M, Nenutil R, Kubanda A, Toufar M, Holub P. Automated annotations of epithelial cells and stroma in hematoxylin-eosin-stained whole-slide images using cytokeratin re-staining. J Pathol Clin Res. 2022 Mar;8(2):129-142. doi: 10.1002/cjp2.249. Epub 2021 Oct 30. PMID: 34716754; PMCID: PMC8822376.

[13] Redmon, Joseph, Santosh Divvala, Ross Girshick, and Ali Farhadi. "You only look once: Unified, real-time object detection." In Proceedings of the IEEE conference on computer vision and pattern recognition, pp. 779-788. 2016.

[14] Mercan, C., Balkenhol, M., Salgado, R. et al. Deep learning for fully-automated nuclear pleomorphism scoring in breast cancer. npj Breast Cancer 8, 120 (2022). https://doi.org/10.1038/s41523-022-00488-w

[15] Wetstein, S.C., de Jong, V.M.T., Stathonikos, N. et al. Deep learning-based breast cancer grading and survival analysis on whole-slide histopathology images. Sci Rep 12, 15102 (2022). https://doi.org/10.1038/s41598-022-19112-9

[16] Campanella, G., Hanna, M.G., Geneslaw, L. et al. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med 25, 1301–1309 (2019). https://doi.org/10.1038/s41591-019-0508-1

[17] Lu, Cheng & Romo, David & Wang, Xiangxue & Janowczyk, Andrew & Ganesan, Shridar & Gilmore, Hannah & Rimm, David & Madabhushi, Anant. (2018). Nuclear shape and orientation features from H&E images predict survival in early-stage estrogen receptor-positive breast cancers. Laboratory Investigation. 98. 1. https://doi.org/10.1038/s41374-018-0095-7

[18] Maqlin, P., Thamburaj, R., Mammen, J.J., Manipadam, M.T. (2015). Automated Nuclear Pleomorphism Scoring in Breast Cancer Histopathology Images Using Deep Neural Networks. In: Prasath, R., Vuppala, A., Kathirvalavakumar, T. (eds) Mining Intelligence and Knowledge Exploration. MIKE 2015. Lecture Notes in Computer Science(), vol 9468. Springer, Cham. https://doi.org/10.1007/978-3-319-26832-3_26

[19] Y. Wang, B. Acs, S. Robertson, B. Liu, L. Solorzano, C. Wählby, J. Hartman, M. Rantalainen, Improved breast cancer histological grading using deep learning, Annals of Oncology,Volume 33, Issue 1,2022,Pages 89-98,ISSN 0923-7534,https://doi.org/10.1016/j.annonc.2021.09.007.(https://www.sciencedirect.com/science/article/pii/S0923753421044860)

[20] Jaroensri, R., Wulczyn, E., Hegde, N. et al. Deep learning models for histologic grading of breast cancer and association with disease prognosis. npj Breast Cancer 8, 113 (2022). https://doi.org/10.1038/s41523-022-00478-y

[21] https://www.morphlelabs.com/