Unveiling the BRCA Gene: Using AI-Driven Medical Imaging Informatics to Revolutionise Cancer Diagnostics

A PROJECT REPORT

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CANDIDATE'S DECLARATION

I am Medha Jha (2K21/IBT/16) student of M.Tech Industrial Biotechnology, hereby certify that the work which is presented in the dissertation titled **"Unveiling the BRCA Gene : Using AI-Driven Medical Imaging Informatics to Revolutionise Cancer Diagnostics"** in fulfilment of the requirement for the award of Degree of Master of Technology in Industrial Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University (Formerly Delhi College of Engineering), New Delhi is an authentic record of my own carried out during a period from January 2023 to May 2023, under the supervision of Yasha Hasija, Department of Biotechnology.

The matter presented in this report has not been submitted or previously formed the basis for the award of any Degree, Diploma, Associateship, Fellowship, or other similar title or recognition.

Date : 13/6/23

Place: Delhi

Medha Jha

CERTIFICATE

I hereby certify that the Project Dissertation titled **"Unveiling the BRCA Gene : Using AI-Driven Medical Imaging Informatics to Revolutionise Cancer Diagnostics"** which is submitted by Medha Jha (2K21/IBT/16) Department of Industrial Biotechnology, Delhi Technological University, New Delhi in partial fulfilment of the requirement for the award of the Degree of Master of Technology is a record of the project work carried out by the students under my supervision and guidance.

To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University/Institute or elsewhere.

Date: 13.06.23

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ABSTRACT

The two most well-known genes inculpated in transcriptional control and DNA repair are breast cancer 1 and breast cancer 2, which are connected to breast tumor, ovarian tumor, and also to lung tumor. In order to elucidate mechanisms by which BRCA genes ultimately lead to the development of breast, ovarian, or lung tumors, the current study set out to clarify the expression patterns, mutational patterns, and interaction pathways of BRCA1 and BRCA2. So here in this thesis bioinformatics tools have been used to analyse these two genes. Artificial intelligence application in image informatics is used. It may enhance therapeutic results and increase the value of medical image analysis in yet-to-be-determined ways. Different techniques of imaging like anatomical (x-ray, MRI, ultrasound) and system generated imaging techniques (microscopy, PACs, SPECT) has been discussed in this paper. FIREHOSE analysis was done to check messanger RNA levels. Breast cancer and Breast cancer 2 mutations were checked using cBioPortal study. A KM plotter study was completed to ascertain the predictive role of these genes in the chosen cancer type. After this box plot and stage plot analysis done with GEPIA2 database to check expression in four stages and for a comparison between normal tissue and tumoric tissue. STRING analysis done to show functional interaction between proteins. Additionally,. Deep learning and machine learning approaches for imaging is discussed at later stage. Deep learning techniques in particular are receiving a lot of attention due to their outstanding efficiency in image-recognition tasks in artificial intelligence (AI). They can more effectively and accurately diagnose patients by performing an automated quantitative assessment of complicated medical image properties. Deep learning, particularly image categorization, is being used more and more in the realm of medical images. For the collection and storage of image data, the Digital Imaging and Communication in medicine is frequently utilized. How OMERO and DICOM database is used for digital imaging is discussed further.

Keywords: breast cancer, lung tumor, ovarian tumor, double strand break, network pathway, artificial intelligence, imaging, deep learning, machine learning, digital pathology

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Description
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
LUSC	Lung Cancer
OV	Ovary Cancer
KM	Kaplan-Mier
DSB	DNA Double Stranded
NHEJ	Non-Homologous End Joining

CHAPTER 1- INTRODUCTION

Breast cancer has become common type of cancer worldwide overtaking lung cancer. It is anticipated that there would be 26.7 million cancer patients in India by 2021 and 29.8 million by 2025[1]. According to current data, Indian women are more likely than Western women to develop the disease while they are younger. Preceding year, the North and Northeast had the highest incidence. One study found that the five year overall survival rate for patients in 1st phase is 95%, 92% for patients in 2nd phase, 70% for patients in 3rd phase, and only 21% for patients in 4th phase[2]. Lung cancer affects non-smokers in some cases. Genetic factors are significant contributor, along with environmental variables like radon, toxins). Various forms of therapy are being used for cure, as cisplatin-based chemotherapy and surgery. Discoveries made in twentieth century made identification and treatment of malignancies more easy. First to employ X rays on tumor patients were Emil Grubbe and Victor Despeignes who identified tumor with stomach and breast [3]. When understanding of radioactivity of materials and methods for isolating them improved, radiotherapy swiftly appeared as a potent tool in the fight against cancer. Radiation with higher doses used to kill the cells of cancer and slow down their growth by destructing their DNA. But there is one issue with the use of radiotherapy that it damages nearby healthy cells too. Images created by medical imaging techniques offer a plethora of data about the morphological characteristics under investigation, making them useful for accurate diagnosis, selecting the most appropriate therapy, tracking the progress of the treatment, and other purposes. Using information and communication technology in field of medical imaging for the delivery of healthcare services is known as medical imaging informatics. The automatic identification of medical images is a particularly challenging work due to the existence of noise and masking structures, variety of biological forms and tissue, imaging system anisotropy. Simplifying the analysis's goal and utilizing some kind of a prior information about the observed structures have always been the solutions to these issues. AI is being used vigorously in cancer studies for automatic cancer and organ segmentation, moreover also AI is used for tumor monitoring for adaptive treatment. These are good grounds of radiological images to develop swiftly, altogether with prominence for AI and the unprecedented supply of image data. Radiomics is a cutting-edge method for addressing the problem of precision medicine. In the long run, we believe that AI will continue to advance

throughout terms of medical decision-making precision in comparison to humans. On the basis of experience users define characteristics of imaging like shape, area or region of interest of tumor. Typically, out of the available data entries, a segment of it used in favor of training and the remainder used in favor of testing. To train on the features, a specific machine learning algorithm is chosen. Deep learning, the most recent generation of artificial intelligence, has made notable scientific advancements over traditional machine learning thus far. Deep learning-based approaches perform significantly better than traditional machine learning approaches. Deep learning acquires its knowledge from a vast number of image examples, much like how humans learn. As opposed to domain expertise, which typically takes years to create, it merely relies on chosen data and the related metadata, therefore it can take considerably less time [4]. Since AI/deep learning has recently achieved progress in image study and the fact that traditional AI requires preset characteristics and has demonstrated plateauing performance in recent years. It's projected that AI will keep dominating radiology's image research. Artificial intelligence and machine learning are an interdisciplinary field that incorporates developments in computer science and neuroscience. The use of machine learning is now commonplace in a variety of industries, providing trustworthy assistance for decision-making and minimizing human work. For the detection of eye sickness, kidney damage, and the management of electronic patient data, Google DeepMind has produced smartphone applications. Machine learning in case of imaging has revealed useful development into different medical fields and has the potential to help practitioners by improving the accuracy and reproducibility of pathology diagnosisWomen possessing BRCA mutations have a 45% to 75% lifelong chance of acquiring breast cancer and an 18% to 40% lifelong risk of developing ovarian tumor [5]. Both these Breast cancer 1 and Breast cancer 2 are tumor suppressor genes and their heterozygous carrier shows a lack of gene's wild-type allele. They play crucial part in activating DNA repair pathways in response to cellular stress [6]. Cells which lack BRCA1 or BRCA2 are not able to cure DSBs through homologous recombination, their repair is initiated instead uses error-prone methods such as non-homologous end-joining [7]. The incidence of BRCA1/2 germline mutations varies by ethnicity and geographical region.

CHAPTER 2: LITERATURE RIVIEW

2.1 BRCA1 and BRCA2 : Gene structure

The BRCA1/2 genes have been vast, complex, and encode proteins involved in a variety of biological functions, particularly DNA repair and the preservation of genomic integrity. Here is a quick summary of how BRCA1 and BRCA2 are structured:

BRCA1:

According to Varol et al.,BRCA1 has 24 exons, which are coding sections, spaced across by introns, which are non-coding regions[8]. The BRCA1 protein is made up of the amino acids that are encoded by the exons.BRCA1 gene present on chromosome 17q12-21 and has 22 coding exons and 2 non coding exons and produces an 1863 amino acid protein, covers aprox. 100kb span of genomic DNA. BRCA1 has a full length mRNA transcript of 8kb along with various small transcript of BRCA1 with a specific pattern of tissue, having 7, 4.6 and 1.5-2.2 kb mRNAs [7]. This domain belongs to RING zinc fingers subclass. BRCA1 is an E3 ubiquitin-protein ligase which preferentially catalyses the creation of polyubiquitin chains with Lys-6 links. BRCA1 performs other cellular activities as duplication of centrosome, assembly of mitotic spindle, remodeling of chromatin and cell cycle control. The following are some of the crucial BRCA1 domains:

- DNA repair and other biological functions depend on the ubiquitin ligase activity of the RING domain, which is also involved in protein-protein interactions.
- BRCA1 (BRCA1 C-Terminal) has two tandem BRCT domains that function in binding DNA and interacting with other proteins. The effective operation of BRCA1 in DNA repair and checkpoint control depends on these domains.
- BRCA1 features a coiled-coil domain that participates in protein-protein interactions and helps to build big protein complexes.

This gene produces nuclear phosphorprotein important for preserving genomic integrity and interacts along histone deacetylase complexes by means of C-terminal domain and RNA polymerase II through its association with the latter. Thus, impact of this protein could be observed in recombination, transcription and DNA double strand break repair.

BRCA2:

Wietzel et al., in his work described that chromosome 13q12.3 in human beings contains BRCA2 gene and BRCA2 encodes for 3418 amino acids[10]. With 3418 amino acids, BRCA2 is much bigger but contains fewer known motifs. They both interact with RAD51 and TP53, have an identical tissue distribution and gene expression pattern. RAD51 helps in repairing DNA double strand and homologous recombination also might take part in checkpoint activation during the S phase. Through the BRC domains, which have been evolutionarily conserved, the BRCA2 protein directly interacts with RAD51.The BRCA2 protein is made up of the amino acids that are encoded by the exons. It shares a number of functional domains with BRCA1 that support its involvement in DNA repair and the preservation of genomic stability:

- Multiple DNA-binding domains on BRCA2 enable it to connect with DNA and speed up DNA repair procedures.
- The short amino acid regions known as BRC repeats, that are abundant in BRCA2, are essential for the protein's binding to the RAD51. For homologous recombination, a DNA repair mechanism, this contact is essential.
- BRCA2 features a number of oligonucleotide/oligosaccharide-binding (OB-fold) domains that participate in protein-protein interactions and are essential for the process of DNA repair.

Murphy et al., in his work described well about both the BRCA1 and BRCA2 proteins help to repair DNA damage, particularly when homologous recombination is involved[11]. These genes are susceptible to mutations that alter their normal operation and hinder DNA repair, raising the likelihood of genetic mistakes and the emergence of cancer.Genetic instability is a result of the extremely high density of repetitive DNA elements in the BRCA1and BRCA2 genomic regions. In outbreaks of breast and ovarian cancer, promoter

hypermethylation may silence the BRCA1 gene. Regular Sanger sequencing of exons and that of the exon-intron junctions is used to screen the BRCA genes.

2.2 BRCA in Breast Cancer

Breast cancer is significantly influenced by the BRCA genes, notably BRCA1 and BRCA2. The risk of developing breast cancer increases when certain genes carry specific dangerous mutations. Balmana et al., described some of the main impacts of BRCA mutations in genes on breast cancer are listed below[12]:

- The chance of developing breast cancer is significantly increased by damaging changes in the BRCA1 or BRCA2 genes. Those with BRCA1 mutations had a lifetime risk of sixty to eighty percent for having breast cancer, compared to four to eighty-four percent for those with BRCA2 mutations. Comparing to the general population, where the lifetime risk of breast cancer is roughly twelve percent, these hazards are much higher.
- Breast cancer with an early onset is linked to BRCA gene mutations. Breast cancer frequently strikes women with BRCA1 or BRCA2 mutations earlier in life, typically before the age of fifty.
- An increased chance of developing cancer in both breasts is also associated with BRCA gene abnormalities. Accordingly, a woman has a greater chance of developing breast cancer in the other breast if she already has it in the first.
- Ovarian cancer risk is increased by the BRCA gene abnormalities, which also dramatically raise breast cancer risk. The lifetime chance of having ovarian cancer is around forty percent for women with BRCA1 mutations and approximately twenty-seven percent for those with BRCA2 mutations.
- Risk of additional malignancies is also elevated by BRCA gene mutations, including the risk of fallopian tubes malignancy, peritoneal malignancy, malignancy of the pancreas, and cancer of the prostate (in the case of BRCA2 mutations). The largest correlation, though, is with ovarian and breast malignancies.

It's crucial to keep in mind that not everyone with a BRCA gene mutation will get breast carcinoma or other related cancers. However, compared to the general population, these mutations greatly raise the risk. Individuals can understand their own risk factors and make

educated decisions regarding surveillance and risk-reduction measures with the aid of genetic counselling and testing. Based on unique conditions and risk factors, routine screenings, like mammograms and MRIs, and preventive interventions, like prophylactic surgeries or chemoprevention, may be advised.Breast cancer 1 and breast cancer 2 mutations in breast tumors can be differentiated using certain pathological criteria. The tumor with BRCA2 mutation is varied, frequently higher, and exhibit fewer tubule formation whereas the tumors associated along BRCA1 mutations are high-grade malignancies having high mitotic index, and pushing tumor borders which are non-infiltrating, smooth edges, and a lymphocytic infiltration. On the basis of percentage of perometer both types of tumors are easily separated from sporadic cases of breast malignancies with continuous pushing margins. Most tumors which contain Breast cancer 1 mutations are often negative for both the estrogen and progesterone receptors, in contrast to the majority of cancers with Breast cancer 2 mutations, which are frequently positive for both hormone receptors [13]. Therefore, these variants show that both the mutant genes contribute to breast cancer development in variety of ways.

2.3 BRCA in ovarian Cancer

Ovarian cancer risk is significantly affected by BRCA gene mutations, especially those in BRCA1 and BRCA2. Paul et al., has given a few outcomes of BRCA genetic changes on cancer of the ovary are listed below[6]:

- The chance of getting ovarian cancer is significantly increased by harmful mutations in the BRCA1 and BRCA2 genes. The lifetime chance of having ovarian cancer is around thirty to sixty percent for women having BRCA1 mutations and approximately one to twenty seven percent for those with BRCA2 mutations. Relative to the wider population, where the lifetime risk of cancer of the ovaries is approximately one to two percent, these hazards are much higher.
- Similar to breast cancer, BRCA gene mutations are linked to earlier ovarian cancer onset; women with BRCA1 or BRCA2 mutations frequently develop ovarian cancer at a younger age than women without these mutations. Increased risk of fallopian tube and peritoneal cancer: BRCA gene mutations also raise the likelihood of

getting malignancies in the fallopian tubes and peritoneum (the lining of the abdominal cavity).

- In particular, BRCA2 mutations are linked to an elevated probability of male breast cancer. In comparison with men without these mutations, men with BRCA2 mutations are more likely to get breast cancer.
- It's crucial to remember that BRCA gene mutations are not the only cause of ovarian cancer; in fact, most cases of the disease affect people who do not have these mutations. However, contrary to the general population, the risk is markedly increased by the existence of BRCA gene mutations. Individuals can make informed choices about surveillance, risk-reduction techniques, and prospective preventative procedures like prophylactic operations with the assistance of genetic counselling and testing.
- For those with BRCA gene mutations, routine screenings and monitoring, such as pelvic exams, transvaginal ultrasounds, and blood tests (CA-125), are sometimes advised to look for any indications of cancer of the ovary at an early stage when treatment outcomes are typically better.

DNA can be altered most commonly by double strand break and can be damaging cells by damaging reading frame which would lead to shortage of a typical reading frame to fix nucleotides to and for these breaks, DNA repair is more challenging. Ovarian tumor genesis may be influenced by oxidative stress during the menstrual cycle. Regulation of hormones, particularly estrogen, does seem to promote DSB, which could account for tissue specificity. A cell can repair a DSB through non-homologous end joining and homologous recombination, respectively. Without taking into account the reading frame, NHEJ induces open ends of the DNA to join binding proteins to stabilize and eventually reunite the sides of the DNA. Single strand 3’ opening is made at the open end which helps proteins like RAD51 or BRCA1 or BRCA2 to search for a sequence and create D-loop and a reading frame is constructed at both the sides. BRCA1 helps in checking the DNA damage as being a part of large molecule complex with large variety of transcript and BRCA2 works in repairing it by attaching RAD51 at repair site. Patients who seem to have gene mutation in either BRCA1/2 are more likely than the general population to develop certain

malignancies and this would increase the risk of tumor growth across a wide range of tissue types.

2.4 BRCA in Lung Cancer

Despite the fact that BRCA mutations are not directly associated to the development of lung cancer, it is crucial to remember that people who have BRCA mutations may still be at risk of getting other malignancies, including lung cancer, due to a variety of variables such as a common risk factor or genetic predisposition. For instance, it has been discovered that people with BRCA2 mutations have a slightly increased chance of contracting multiple tumours, such as carcinoma of the pancreas and carcinoma of the prostate.Accordimg to Vinay et al., BRCA1 is involved in TC-NER, or transcription-coupled nucleotide excision repair, and altering BRCA1 expression alters TC-NER, which results in radio- and chemoresistance[14]. Through the C-Junction N-terminal kinase pathway, which itself is initiated by cisplatin-induced DNA damage, increased BRCA1 expression has been connected to apoptosis and suppression of this pathway has improved cisplatin sensitivity in cell lines. The two recognized most important susceptibility syndromes for lung cancer are Li-Fraumeni and EGFR-associated susceptibility syndrome. Li-Fraumeni is caused by germline pathogenic variant in the TP53 gene which leads to elevated threat of budding multiple types of cancer, often at a young age, including lung cancer. EGFR-associated susceptibility syndrome is induced by activating variant in EGFR gene and leads to development of lung cancer in adulthood.

Table 1: Different analytical Techniques used for detecting Cancer

Reference	Focus of the paper	Techniques used	Analysis	Research gap
M.B et al.[15]	BRCA1/2 mutation screening for breast and ovarian cancer	Mutation screening,laser-capture microdissection (LCM), Denaturing high-performance liquid	Mutation analysis, LOH analysis	First report of a LOH for BRCA2 study in primary lung adenocarcinoma tissue from a patient with

		chromatography		multiple primary tumors caused by a familial hereditary BRCA2 mutation. Surprisingly, the mutant allele was lost in lung cancer tissue rather than the wild-type allele
O'Sullivan et al. [16]	PARPi activity with BRCA for lung, breast, prostate and ovarian cancer	Gene fusion, clinical trial, HR/PARP lethality model, biomarkers	Anti tumor activity	PARPi are a type of drugs with modes of action that extend beyond their known activity in the BER pathway. They could have a broader impact in the therapy of individuals with cancer
Thorne et al. [11]	comparision of metastatic disease from autopsy of patients with breast, and ovarian tumor without and with inherited BRCA mutations.	CASCADE program, Fisher's exact test	Statistical analysis, metastatic analysis of carrier and non-carrier	The main disadvantage of this research is that the sample size is tiny, especially when looking at tumor types independently, underscoring the logistical difficulty of doing such investigations.
Wang et al. [18]	Expression and mutation of BRCA	FIREHOSE, SAGE	Oncomine analysis, Kaplan-Mier analysis	The findings not only show that the BRCA1/2 genes are overexpressed

				in ovarian and breast cancer, but also shed light on the mutations and interaction networks of these two genes.
Yang et al. [19]	LCN1 biomarker for breast cancer by bioinformatic analysis	Kaplan–Meier plotter	UALCAN database analysis	confirmed LCN1's importance in BRCA, indicating that it might be a useful biomarker for BRCA diagnosis
Thery et al. [14]	Bioinformatic prediction of unclassified variants of BRCA	Minigene-based splicing assays	variants of unknown significance	It is possible to boost the specificity of bioinformatics predictions by demanding a greater percentage of score variation and perhaps by considering not just not just the variation's percentage, but also the natural splice site's tensile strength
An et al. [21]	Bioinformatic analysis of zinc finger protein	Multi-omics bioinformatics	Correlation analysis, methylation, pathway analysis	A multimodal investigation of the BRCA ZNF family genes conducted, including analyses of differential expression, prognosis, immunological subtypes, tumour microenvironment, and methylation

Shuaicheand Guangyi et al. [22]	Bioinformatic analysis of CYP2C9	GEO database, GEO2R	Protein-Protein interaction, Gene ontology	This bioinformatic research show that DEGs, particularly those involved in drug metabolism, including CYP2C9, may encourage the growth of HCC. Additionally, it might serve as a brand-new biomarker for diagnosis
Li et al. [17]	Bioinformatic analysis of CALR	COSMIC, GeneCard, GEPIA, UALCAN	CALR expression analysis	As a biomarker for prognosis and a possible target for tumour molecular and immunotherapy, CALR can be employed. Immune cells in general are intimately related to CALR.

2.5 DEEP LEARNING

Deep learning technology, which could automatically discover characteristics from data by Deep learning is now being employed extensively in the realm of medical images recently. training large-scale datasets, has significantly advanced computer vision compared to human feature extraction. Deep learning, particularly image categorization, is being used more and more in the realm of medical images.Deep neural networks may automatically learn characteristics from training data, demonstrating improved efficiency and classification accuracy, according to recent studies [24]. Numerous artificial neuronal layers that closely resemble the neurons in the human brain make up deep learning (also

known as DNN). Similar to linear regression, backpropagation using the gradient descent technique updates each neuron's weight value to reduce the overall loss function[25]. It was possible to extract more abstract mathematical relationships from the input data to transfer to the output by applying nonlinearity utilising activation functions, to the numerous layers of each neuron. Therefore, fresh unlabeled data can be predicted using a well-trained model.Deep learning, an intriguing and potent subfield of machine learning, has recently outperformed more traditional ML methods in handling pattern recognition and computer vision challenges. Deep learning is used with domain adaptation for medical imaging. Basically, two approaches are used: one in which image is translated from one domain to another using domain transformation which helps to make such models which can be directly applied to images. Whereas in second approach latent feature space transformation is used in which image is aligned to both the domains and common features are used for imaging. Images are translated using domain transformation-domain adaptation from one domain to another. Such translation is frequently carried out using generative models, which learn the translations at a semantic level and then map it to pixels.It can do this by enhancing interpretability, aligning the space of image rather than the space of feature sets, maintaining low-level appearance features using structure and structural-similarity restrictions, and visual inspection of synthesised images. Unidirectional translation converts images from the source domain to the destination domain or likewise using a generative adversarial network. The dataset variations have been eliminated via unidirectional translation. Bidirectional picture translation reduces the mapping space by enforcing semantic consistency between the original and rebuilt images using two generative adversarial networks [26]. The automatic development of this set of features without human involvement has several benefits in fields like health informatics. For example, it can provide aspects that are more complex and challenging for articulating in descriptive ways in medical imaging. Such a characteristic in convolutional neural network (CNN) can be understood as learning hierarchical data representation. One specific kind of neural network is convolutional neural network . For classification purposes, it typically consists of three layers:

- Convolutional layer
- Down-sampling layer, and

- Final fully linked layer

The most crucial component is typically the distinct convolutional element, which seeks to identify and extract characteristics from the input data. The final fully connected layer makes a determination regarding which class the input photos may belong to after the pooling layer acts as a data reduction method.By iteratively repeating the convolution and pooling layers, a CNN can go deep.Deep learning's practical adoption and acceleration have both been significantly impacted by recent advancements of graphics processing units (GPUs).Deep learning systems like CNNs can be highly parallelized by moving the majority of simple algebraic operations with dense matrices to the GPU, including matrix products and convolutions. By requiring the network to change a set of parameters during back-propagation which are equivalent about one instance of the filter, a CNN significantly reduces the connections from a normal NN architecture. The neurobiological model of the visual cortex is an important server for the CNN concept. There are several issues that need to be handled when applying deep learning to health informatics. For instance, obtaining the quantity of labeled data necessary to train a deep architecture can be challenging in the healthcare industry. Additionally, deep learning needs a lot of computer power, because without it training could take too long. Additionally, in order to overcome the difficulties of convergence issues and over fitting, new learning strategies are required.

Ali et al., described abouta multivariate semi-parametric regression model called the Cox proportional hazards model, which has been extensively utilised in cancer studies to assess survival traits across multiple treatment groups[27]. These research examined the efficacy of NN to Cox-PH and/or Kaplan Meier methods to demonstrate performance, and they demonstrated that simple NN models had comparable performance to these methods. Cox-nnet is a NN network that uses Cox regression as the output layer and genomic data from TCGA as the input layer.

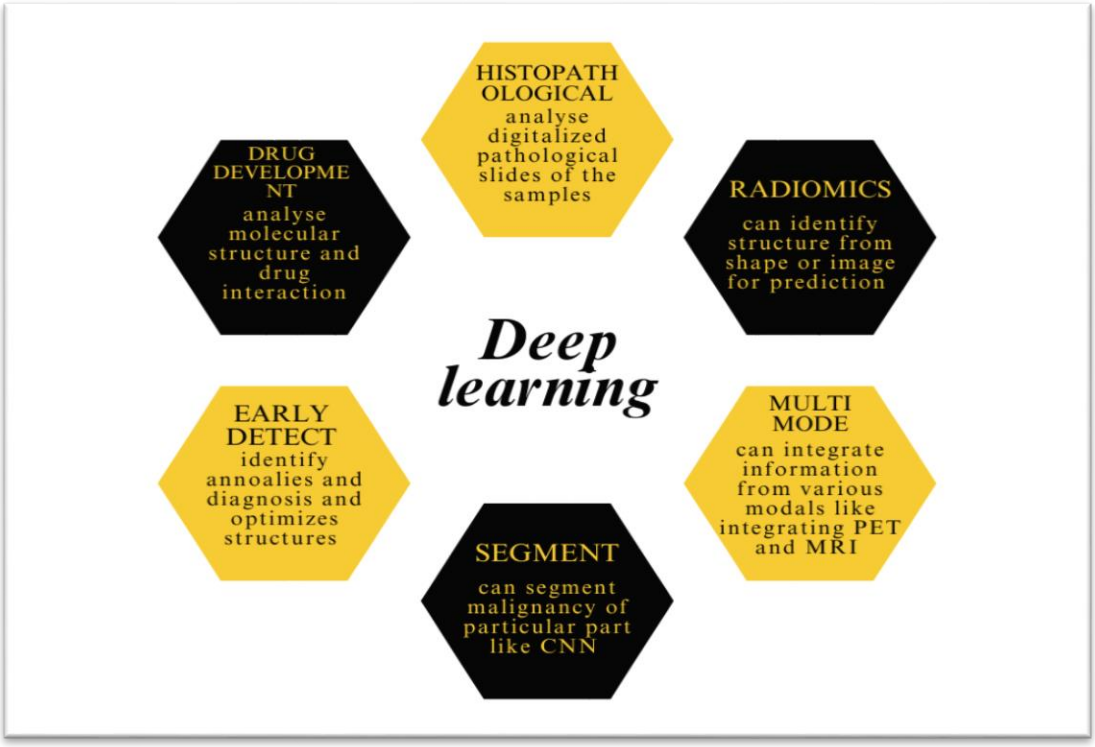


Figure 1: Deep learning features

2.5 ML for tumor

There is considerable interest in using machine learning for diagnostic, prognosis, and treatment issues in the field of oncology. For instance, the IBM Watson for Oncology i.e WFO system has proven to be successful at recommending treatments for particular cancer patients Tang et al., demonstrated models based on the characteristics of the patient, which can predict outcomes by learning patterns and traits associated with various cancer kinds[28].By examining patient-specific data, such as genetic profiles, clinical data, and therapy outcomes, ML models can help in treatment selection. ML can identify therapy responses, recommend personalised medicines, and optimise treatment approaches based on unique patient features by utilising vast datasets and powerful algorithms.ML models have the ability to forecast drug molecule function, pinpoint possible drug targets, and enhance drug characteristics. Large-scale metabolic, proteomic and genomic and proteomic datasets can be examined using machine learning algorithms to find potential cancer biomarkers.Based on the characteristics of the patient, ML models can predict outcomes by learning patterns and traits associated with various cancer kinds.By examining patient-specific data, such as genetic profiles,

clinical data, and therapy outcomes, ML models can help in treatment selection. ML can identify therapy responses, recommend personalised medicines, and optimise treatment approaches based on unique patient features by utilising vast datasets and powerful algorithms.ML models have the ability to forecast drug molecule function, pinpoint possible drug targets, and enhance drug characteristics. Large-scale metabolic, proteomic and genomic and proteomic datasets can be examined using machine learning algorithms to find potential cancer biomarkers.

In order to find papers that are well matched to the features of particular patients, WFO was able to learn an enormous corpus of medical journal, textbook, and treatment guidelines material in the field of breast cancer at Memorial Sloan Kettering Cancer Center. Additionally, it included information from more than 550 breast cancer patients at MSKCC, including aspects of the patient, their functional state, the features of the tumour, their stage, and imaging as well as other laboratory results [29]. With professional input, WFO can improve its analysis procedure even more. A single patient can now receive advice for treatment planning and alternate possibilities within each medication regimen from the system. In general, there are two basic categories of imaging acquisitions: anatomical imaging, which includes standard X-rays, ultrasounds, CT scans, and MRIs, among other things, another is molecular imaging, which includes diffusion-weighted MRI, SPECT, and PET. Multimodality imaging combines the benefits of anatomical resolution and tissue functional information. Additionally, methods like SPECT/CT, PET/CT, and PET/MRI were developed. With all these methods at hand, photos can offer significant information about the tumour, its environment, and the patient's genotype that can be data mined to aid in the diagnosis, prognosis, and prediction of oncology outcomes. If for instance brain tumor is diagnosed with help of machine learning then prior to applying morphological operations, an image subtraction technique is used for obtaining tumor region. The MRI brain images are first preprocessed with a median filter, threshold segmentation, and image segmentation to get the shape of it. Principal Component Analysis is used to extract features from an MRI brain picture, and Multi-Layer Perceptron is then utilised to categorise the retrieved features. MRI scans are utilised to identify brain tumours using an image segmentation technique, followed by the automatic classification of brain tumours using Probabilistic Neural Networks. The proposed PNN approach offers

more accurate brain tumour classification. Gray-Level Co-occurrence Matrix is used to extract the textural features, and Self-Organizing Maps are utilised to categorise the brain as normal or abnormal, i.e., whether or not it contains tumors [30].

2.7 DIGITAL PATHOLOGY

Pathological specimens are examined under a microscope by labeling them using colorimetric dyes or antibodies. Multiple high resolution imaging could offer details on level of protein expression and sub cellular localization, enabling molecular profiling to tissues while preserving the original tissue architecture. This makes it possible to examine the statuses of cells, tissue biomarkers, and interactions between cells in both healthy and pathological settings. Currently, tissue samples taken from surgical resections or biopsies are fixed with formaldehyde, or embedded with paraffin, shrugged into five mm-thick slices, and marked with hematoxylin and also with eosin. In order to perform fast analysis, specimens are segmented, stained, and frozen. Pathologists have recently begun using machine learning algorithms' pattern identification capabilities to gain deeper diagnostic insight from histology data. In the recent years, ML algorithms have improved and expanded to the point where they are now used to assist in the understanding of smeared slides, which clinicopathologic laboratories analyse in large quantities. Additionally, they have sparked the growth of numerous start-ups and tools for digital pathology. Imported and system generated data used for analysis. For the collection and storage of image data, the Digital Imaging and Communication in medicine is frequently utilised. Considering the patient as the foundation Within ANALYSIS, DICOM data may be manipulated by utilising DICOM data hierarchy [31]. The open-source image-informatics system OMERO is the most extensively used and is interoperable with a variety of software clients. The server becomes severely overloaded as photos get bigger, this restrict the amount of concurrent sessions. Client needs connectivity to an OMERO database [32]. Project Mirador makes use of database-free viewers that are built on the free and open-source OpenSeadragon framework it makes zooming and panning across photos simple.

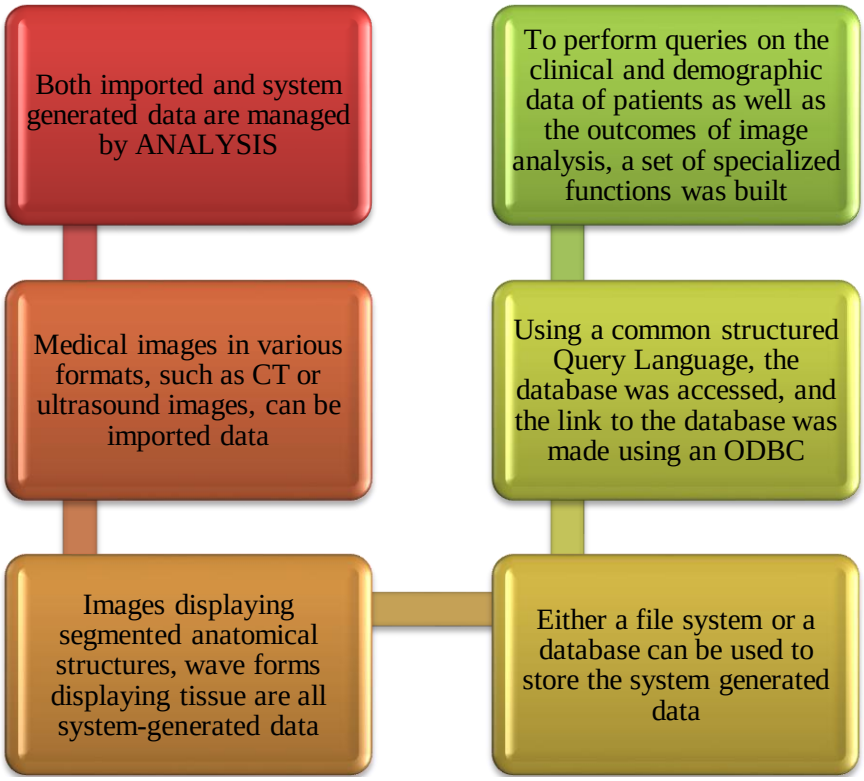


Figure 2 : steps for imaging of tumor[32]

2.8 IMAGING IN REGENERATIVE MEDICINE

Through the use of particular cell populations, either by themselves or in combination with biomaterial scaffolds, regenerative medicine seeks to restore the function of damaged tissues while accelerating the body's natural ability to mend itself. Here, clinical imaging is essential for identifying injured tissue and evaluating the safety and effectiveness of treatment. Imaging is frequently utilised in clinical practice to give secondary endpoints that support primary health outcomes and to look into the mechanisms underlying successful and unsuccessful treatment interventions. New opportunities in regenerative medicine are provided by the newest clinical scanners, which can be used to monitor transplanted cells, analyse the tissue composition of organs, and measure the impact of therapy on tissue function. They are starting to be used to evaluate cell therapy's underlying mechanisms as well as the transplanted cells' survival, migration, biodistribution, and differentiation without causing any harm to the patient. A good option for in vivo stem cell research is the recently established spectral encoding of the spatial frequency (SESF)

technique, which enables label-free viewing of the internal nanometre structures in actual time with nanoscale sensitivity.

Benefits and challenges of using imaging in regenerative medicine are following:-

- Researchers need to make sure that subjects who have been approved will tolerate imaging tests. Imaging is crucial for figuring out whether or not people match the requirements for inclusion or exclusion in clinical trials for research participants should include imaging results.
- Choosing the ideal administration route requires imaging.
- When determining if the targeted area can sustain the cell graft, multimodal imaging is useful.
- Using clinical imaging to ascertain the efficacy, volume of distribution, and longevity of the cell product and to create a delivery plan for patients presents a difficulty. Clinical studies will benefit from mechanistic insights provided by new labels that track the destiny and functioning of cell products.
- The ideal modality must offer in situ, depth-resolved, non-invasive imaging, be able to identify single cells, and distinguish between cell death and proliferation.

CHAPTER 3: MATERIAL AND METHOD

3.1 FIREHOSE Analysis

The Broad Institute has provided a web based portal that is FireBrowse portal used to look at the expression profile of the genes in diverse forms of the tumor. Breast cancer 1/2 was entered to the search bar on the webpage, and the option to view the expression profile was chosen. (http://firebrowse.org/). Shown in figure 1.

Firehose analysis, as used in relation to bioinformatics and the BRCA gene, can be defined as the examination of extensive genomic data obtained from a variety of sources, including microarrays, NGS and various other high-throughput techniques. The phrase "firehose" refers to the large amount of data that must be processed and analysed in a continuous flow.In the area of BRCA gene study, firehose analysis often entails the subsequent actions:

- Public databases or lab studies are used to create genomic data relevant to the BRCA gene, such as DNA sequencing, gene expression, or genetic variation data.
- In order to maintain consistency and comparability, the raw data gathered from multiple sources frequently needs to be preprocessed in order to remove artefacts, account for biases, and normalise the data.
- When dealing with DNA sequencing data, variant calling techniques are used to find BRCA gene-specific variants (mutations or genetic variations). This entails identifying changes or mutations by contrasting the sequenced DNA with a reference genome.
- To acquire a thorough understanding of the BRCA gene and its connection to breast cancer, several types of data, including gene expression data, clinical details, and genetic variations, can be integrated. This could entail determining the patterns of gene expression linked to BRCA mutations or evaluating the effect of certain mutations on gene expression.
- To find significant relationships, correlations, or patterns in the BRCA gene data, statistical approaches and machine learning techniques are used. Finding differentially expressed genes, evaluating the effects of particular mutations on

protein function, or forecasting patient outcomes based on genetic differences may all be part of this.

Bioinformatics FIREHOSE analysis helps researchers better understand the functional effects of BRCA gene mutations, find possible therapeutic targets, and develop risk assessment and individualised treatment plans for people with these mutations.

3.2 Kaplan-Mier Plotter:

The analytical significance of the genes of BRCA1/2 in ovarian, lung, and breast malignancies was examined using the Kaplan-Meier Plotter. The main goal of the tool is the discovery and validation of survival biomarkers for cancer research on the basis of meta-analyses. The Kaplan Meier plotter can analyze more than thirty thousand samples from twenty-one tumor types, including breast, lung, ovarian, gastric cancer to determine the relationship between the expressions of all genes like mRNA, protein or miRNA analysis. (https://kmplot.com/). Shown in figure 2.

A popular bioinformatics tool for survival analysis in cancer research, such as that on breast cancer and the BRCA gene, is the Kaplan-Meier plotter. It enables scientists to evaluate the relationship between particular genes, such as BRCA1 and BRCA2, and patient survival rates.The Kaplan-Meier plotter combines clinical data, such as patient survival rates and illness progression, with gene expression data from large-scale genomic datasets. It makes it possible to create Kaplan-Meier survival graphs, which show how likely it is for various patient groups to survive over time based on the amount of gene expression.We normally need to submit gene expression data or choose the BRCA1 or BRCA2 genes of interest in order to use the Kaplan-Meier plotter for BRCA gene research. The application then creates survival curves for each group after stratifying patients into several groups based on high or low gene expression levels. Researchers can ascertain whether patient outcomes are correlated with the expression of a particular BRCA gene by comparing the survival curves.Additional elements of the Kaplan-Meier plotter may include subgroup analyses based on particular clinical criteria (such as tumour stage or hormone receptor status), as well as the capacity to assess the effect of gene co-expression or genetic changes on patient survival.

3.3 Box plot and Stage plot Analysis*:*

Box plot and stage plot analysis in bioinformatics can be used to investigate the association between the BRCA gene and different clinical characteristics, such as tumour stage in breast cancer. These evaluations aid in determining the relationship between various illness stages and BRCA gene expression or mutations.The GEPIA2 database also yielded information on BRCA1 and BRCA2 gene expression in box plots and based on the pathological phases of BRCA, LUSC, and OV. Similar to this, the over expression of the breast cancer 1 and breast cancer 2 genes was assessed into various clinical stages of BRCA, LUSC and OV depicted by the violin plot (Figure:3 C and D). The probability that the F statistic, Pr > F, will occur was 1e-33 for BRCA1 and 5.05e-13 for BRCA2, and the F test value was 41.9 for BRCA1 and 16.2 for BRCA2. Here, box plots show how much or how far the four cancer stages of the disease have spread. Compared to the skinnier area at the end, the wider middle portion resembles a higher chance of expression around the median value. (http://gepia2.cancer-pku.cn/).

Box plots can be used to show how the BRCA gene expression levels vary depending on the stage of the tumour. Large-scale genomic databases can provide information on gene expression, and clinical data can provide details on tumour stage. It can be used to visualise the median, quartiles, and any outliers of BRCA gene expression for every phase of tumour development. The spread of levels of gene expression throughout stages can be compared to spot any noteworthy variations or patterns that might point to possible correlations among the BRCA gene and tumour stage.The stage plot study looks at the occurrence of BRCA gene mutations or other genetic changes throughout several stages of tumour development. This investigation helps establish whether a link exists between the advancement of tumour stage and BRCA gene mutations.

Resources for mutation annotation or genomic databases can be used to find information about genetic alterations in the BRCA gene. Clinical statistics or research can be used to determine the tumour stage.

Stage plots typically show each tumour sample as a data point, with colour or form designating the occurrence or omission of BRCA gene mutations or changes. The tumour stage-based grouping of the data points enables the visualisation of mutations frequency

bands within each stage.Researchers can better comprehend the connection among the BRCA gene and clinical traits, like tumour stage, in breast cancer by using both box plot and stage plot analysis. These visualisations help in finding potential correlations, highlighting variations in gene expression or mutation rates between phases, and gaining understanding of the BRCA gene's function in the development of disease.

3.4 STRING Analysis:

STRING analysis was done to show functional interaction between proteins. The investigation of protein-protein interactions and functional relationships across genes or proteins, including the BRCA gene, is made easier by the widely used bioinformatics tool STRING. Using data from experiments, co-expression patterns, text mining, and algorithmic predictions, STRING combines data from numerous sources to forecast protein-protein interactions.STRING, shows proteins with a strong to very strong positive connection with BRCA1 and BRCA2 in the majority of malignancies and certain tumour suppressors. (https://string-db.org/) shown in Figure 4.

We can carry out a variety of analyses while utilising STRING for BRCA gene analysis. STRING may produce a network representation of protein-protein interactions involving BRCA gene products for PPI network analysis. STRING retrieves known and anticipated interactions with other proteins based on the input of the BRCA gene or protein IDs. The generated network can shed light on the molecular pathways and functional interactions involving the BRCA gene. STRING enables the discovery of enriched biological processes or functional annotations connected to the BRCA gene. STRING may do enrichment analysis utilising Gene Ontology (GO) keywords or other functional databases by providing the BRCA gene set. This analysis aids in identifying biological concepts and procedures associated with the BRCA gene. STRING retrieves known and anticipated interaction partners after the BRCA gene or protein identifiers are entered. This investigation can show the proteins that interact with the BRCA gene's by direct or indirect means and may impact how the gene functions.

Using STRING's interactive visualisation tools, you may explore and see the PPI networks connected to the BRCA gene. Researchers can evaluate the connectivity, clustering, and

functional relationships of proteins interacting with BRCA gene products using the network visualisation.In order to make the results easier to understand, STRING provides a variety of visual representations and statistical scores, such as node colouring based on evidence kinds, confidence scores for interactions between proteins, and enriched p-values for functional annotations.Researchers can better comprehend the interactions between proteins, functional connections, and biological processes involving the BRCA gene by using STRING for BRCA genome analysis. This knowledge can aid in the discovery of possible BRCA gene-related biological functions, interaction partners, and therapeutic targets.

3.5 COSMIC Analysis:

The BRCA gene is one of many somatic mutations that can be identified in cancer, according to the comprehensive database COSMIC. It lists genetic changes discovered through genome sequencing analyses of tumour samples, such as deletion, copy number variation, mutation. These charts show the frequency of mutations in each cancer type, as well as the distribution of coding strand substitutions in the BRCA1 and BRCA2 genes. These informations are useful in understanding the patterns of genetic mutations related with various types of tumor and can inform the development of targeted therapies. (https://cancer.sanger.ac.uk/cosmic) shown below.At website COSMIC offers two versions: one that is free to use and one that requires a subscription and has more sophisticated capabilities. so first we locate the BRCA gene in the COSMIC database by using the query function or gene-specific filters. Depending on whatever particular gene we want to analyse, the gene is either labelled BRCA1 or BRCA2. Once the BRCA gene has been determined, we can access data pertaining to the somatic mutations that have been found in this gene across a variety of cancer types. The exact mutation, the cancer type in which it was discovered, the sample size, and the relevant references are all details provided by COSMIC.Examine the COSMIC mutation features linked to the BRCA gene to analyse mutation characteristics. It may involve the mutation's kind (missense, nonsense, or frameshift, for example), where it takes place in the genome (exon or intron), as well as how frequently it occurs in various cancer types. It could provide details on the effects of particular BRCA gene mutations. Comments describing if a mutation is likely to be

harmful or might influence protein function can be included in this.The BRCA gene's somatic mutation landscape can be investigated using COSMIC, and its importance in cancer can be understood. It offers a lot of information that can aid in studies, clinical choices, and the creation of specialised treatments for cancers linked to BRCA.COSMIC Analysis is done which displays graphs showing the division of a variety of Breast cancer 1 and Breast cancer 2 mutation types in all three cancers. An outline of a variety of mutations that have been discovered in sample for this gene is provided in the chart in this section. The table lists the number of samples that were identified as having a specific type of mutation along with the proportion of samples that had that mutation.

Table 2: BRCA1 and BRCA2 mutation distribution in breast cancer

Mutation type	Number of samples (BRCA1)	Percentage	Number of samples (BRCA2)	Percentage
Nonsense substitution	25	9.69%	41	12.02%
Inframe insertion	0	0.00%	1	0.29%
Missense substitution	120	46.51%	183	53.67%
Frameshift deletion	35	13.57%	54	15.84%
Frameshift insertion	19	7.36%	14	4.11%
Synonymous substitution	11	4.26%	13	3.81%
Complex mutation	1	0.39%	3	0.88%
Inframe deletion	3	1.16%	5	1.47%

Table 3 : BRCA1 and BRCA2 mutation in lung cancer

Mutation type	Number of samples (BRCA1)	Percentage	Number of samples (BRCA2)	Percentage
Nonsense substitution	1	0.69%	24	9.20%
Inframe insertion	0	0.00%	2	0.77%
Missense	24	23.08%	186	71.26%

substitution				
Frameshift deletion	1	0.00%	8	3.07%
Frameshift insertion	0	0.00%	5	1.92%
Synonymous substitution	7	6.73%	27	10.34%
Complex mutation	0	0.00%	0	0.00%
Inframe deletion	0	0.96%	0	0.00%

Table 4 : BRCA1 and BRCA2 mutation distribution in ovary cancer

Mutation type	Number of samples (BRCA1)	Percentage	Number of samples (BRCA2)	Percentage
Nonsense mutation	0	0.00%	24	9.20%
Inframe insertion	0	0.00%	2	0.77%
Missense substitution	3	100.00%	186	71.26%
Frameshift deletion	0	0.00%	8	3.07%
Frameshift insertion	0	0.00%	5	1.92%
Synonymous substitution	0	0.00%	27	10.34%
Complex mutation	0	0.00%	0	0.00%
Inframe deletion	0	0.00%	0	0.00%

3.6 BIOMEDICAL IMAGING METHODS

Medical therapy has altered as a result of the ability to identify disease utilizing body imaging, cells with high visualization, and pathological specimen analysis. Continued acquisitions at greater rates and reduced radiation dose for anatomical imaging technologies are among the difficulties and possibilities in the field of biomedical imaging. At one end of the range, radiation having a high energy but shorter wavelengths like X and gamma rays creates ionizing images, whereas radiation with longer wavelengths like optical and still greater wavelengths like MRI and ultrasound creates non-ionizing images.

In the recent years, the technique of magnetic resonance imaging (MRI) has seen constant development, leading to MR systems with more potent radiofrequency transmission coils and also with higher static magnetic fields. when used with radio frequency it produces high resolution images of hydrogen nuclei. Cardiovascular imaging is one area of medicine where MRI is being utilised more frequently, therefore thorough patient screening prior to the scan, accurate risk assessment, and skilled patient management are essential[33]. Nanoscale MRI has the ability to produce contrast through selective isotope labelling, real 3D subsurface imaging, and nondestructive operation. It is well known as a potent method for obtaining 3D physiological and morphological information in medicine and the behavioral sciences.

Image reconstruction is made easier by the magnetic resonance force microscopy (MRFM) by tip-sample interaction's slice selectivity which is crucial component of medical MRI. Whereas in conventional force microscopy, the interaction of the sample and the tip gets stronger as it gets closer. The largest interaction, however, occurs in MRFM studies with spins that are positioned far away from the tip, where the spin oscillation frequency coincides with the applied radio frequency field. A rapidly evolving technology for evaluating the shear modulus of tissues and quantifying the mechanical characteristics of tissue is magnetic resonance elastography . The most significant early clinical application of the technology has been for noninvasively detecting hepatic fibrosis, particularly enhances the rigidity of liver tissue. The method is now available as an upgrade to ordinary MRI scanners.

Chest X-rays and computed tomography scans are frequently used as screening techniques in clinical practice. Due to their inexpensive cost and ability to quickly assess patients' lungs at the bedside, chest X-rays are being used as portable instruments for many years. Radiologists spend the majority of their time manually analysing the collected images, which is labor- and time-intensive. Therefore, the creation of computer-aided diagnosis tools is of great importance. It has been utilised quite frequently recently, especially to help with the early diagnosis of pneumonia associated to Covid-19 from medical pictures [34]. It also helps in detection of diseases like cardiothoracic or intestinal disease. X-rays are passed through the body and one detecting array is present on the other side which captures the two dimensional image with 100 micron resolution.

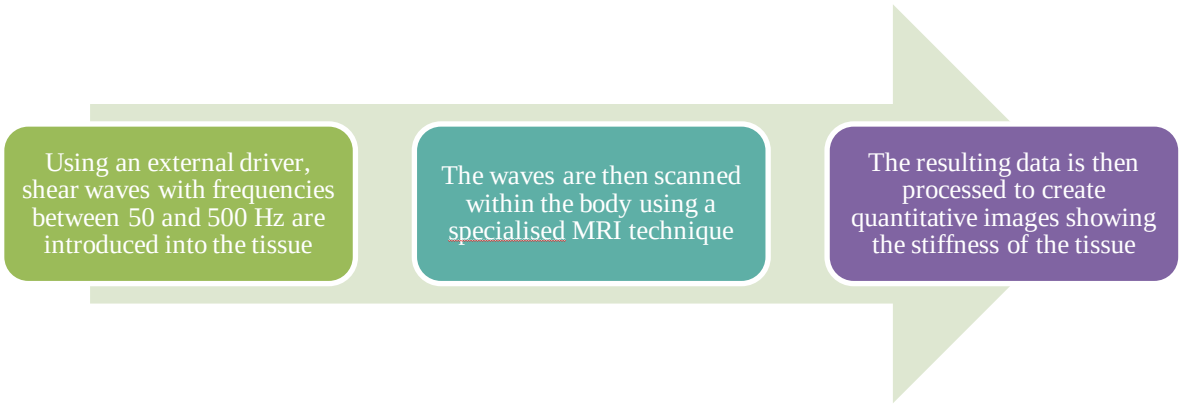


Figure 3: steps for MRI

The most important part of any ultrasonic imaging system is the transducer. The majority of the piezoelectric materials used in clinical transducers, such as lead zirconate titanate, are artificial ferroelectric ceramics [35]. Characteristics of the appropriate transducer for ultrasonic imaging should be precisely matching to the human body with highly efficient transmitter and a receiver, a broad frequency response for pulse operation and a broad dynamic range. In ultrasonic imaging, the beam can be moved mechanically by moving a single component or electronically by controlling an array of transducers made up of many small elements.The 2-D scan plane created with 1-D linear, phased, or curved array for three-dimensional imaging can be mechanically brushed, either linearly in the orthogonal direction or via a sector. Multiple transmitting beams can be created concurrently for real-time 3-D scanning; each transmitting beam could either be connected with a single receiving beam or, by widening the transmitting beam, can support multiple narrowly concentrated receiving beams.

Reflex transmission imaging is has been used in medical imaging since long.Utilizing this novel imaging RTI method, orthographic transmit images can be produced using boosted b-mode equipment. Due to this phenomena, insonification techniques that removed diffraction aberrations and enabled smoother blurred or soft images features at the same time as keeping crisp focus inside the focal plane were developed. Here in this method focal zone of an ultrasonic beam could be moved along tissue that could be imaged while backscattered echoes from a tissue volume outside of it are integrated and presented. Additionally, incoherence is required for reflex transmission imaging, which the tissues' irregular reflectivity provides. Although b-scanning uses ripple effects from inside the body

that are enlarged, recognised, and exhibited as a result of the moment, which corresponds to depth, physical or electrical imaging adds another dimension to the image [36]. The attenuation of the tissue in the focal volume dominates the received signal's amplitude.

Fewer measurements in fluorescence microscopy suggest less light staining on the specimen, lowering destruction of tissue and fluorophores photobleaching brought on with overexposure.Numerous optical sectioning techniques have been devised to collect light just from the plane of a particular sample because bulky specimen emit radiation simultaneously from both the lighted volume in its entirety and the focused plane. In terms of pivotal resolution, the collected image decreases as a result ofgathering blurry light because it lowers contrast. Numerous optical sectioning techniques have been devised to collect light justfrom the plane of a particular sample because bulky specimen emit radiation simultaneously from both the in-focus plane and the full illuminated volume. The pivotal resolution of the collected image decreases as a result of collecting out-of-focus light since it reduces contrast [37]. It has been demonstrated that the optical sectioning strength of the confocal microscope, which uses point detection and illumination, is a total mean cumulative behaviour of each of the elements of illumination structure where aconfocal microscopy employs a raster scan technique and places a pinhole in front of the detector in a plane conjugated with the sample to reject blurry light, moving sensor focal spot over the whole specimen in the image plane. After that, the axial direction can be used to scan the profundity of the imaging plane.

The high-energy photons that the patient emits are collected by the detectors in the SPECT system, which also estimates its position of interaction and energy, and produce count data for eventual picture restoration.A single crystal that absorbs incident gamma photons and scintillates or emits light in response, along with banks of photomultiplier tubes and devices to evaluate the energy of the gamma rays and the location of the scintillation within the crystal, are the foundation of the majority of SPECT systems. These cameras rotate around the patient's body. Energy resolution affects image quality. Their layout, composition, and electronics determine how well they can carry out these tasks. The main factors that determine a SPECT detector's performance are energy resolution, lens sensitivity, and spatial resolution. The more successfully core from scattered photons can be distinguished by an imaging instrument, the stronger the image quality and the more

precise quantification of the radionuclide's concentration and distribution in vivo.The image reconstruction procedure also affects the system spatial resolution for all SPECT imaging instruments. Filtered backprojection, which combines a reconstruction kernel with a postfilter that is often made to reduce picture noise, is the most widely used reconstruction algorithm.

A broad definition of medical imaging informatics includes aspects relating to PACS, image processing, and analysis applications, in addition to informatics concerns. The technique of radiology has been transformed by PACS, which is based on digital communication, display, andinformation technology. When used in conjunction with medical imaging informatics, it significantly improves clinical care. PACS is now a very important part of the modern healthcare delivery system across the board. The management, archiving, and distribution of digital pictures as of x-ray, CT, MRI and ultrasound imaging devices are made possible by the PACS information system, which is used by diagnostic imaging services. The major parts of a PAC are:-

- Server
- Communication Infrastructure
- Acquisition Interface
- Storage System

One component of the PACs is the server, and another is the acquisition interfaces for digitally capturing radiological images. Such photos are converted to common formatstored onto PACS server. Additionally, it displays working places that access the medical imaging from the server of PACS and displays it to the clinician, radiologist, or technologist as well as storage systems that offer long-term, permanent storage for radiology images and a communications network that enables information sharing between the various system components.

Table 5 : Comparision between different techniques

Serial no.	Imaging techniques	Application	Advantages	Disadvantages	References
1	MRI	Breast and brain tumor	Quantitative imaging, massive	Strong magnets might affect	[33]

			database generation using models		
2	MRFM	Hepatic fibrosis, Ovary tumor	Image reconstruction is easy	Sensitivity, has a large computational need and is new for clinical technicians	
3	X- rays	Pneumonia (Covid), cardiothoracic, intestinal disease	Inexpensive	Multiple radiations can be harmful	[38]
4	Ultrasonic Imaging	Fetal imaging	Real time 3D scanning and fast	Penetration is limited and requires skilled people	[39]
5	RTI	Images of various organs	Multimodal imaging	Needs stable source for lighting and any error in this might affect result. Also, this technique is limited to surface detection	[40]
6	SPECT	Oncology	Produce 2D image that can be combined with 3D image, In one single	Spatial resolution and sensitivity is low with respect to other imaging	[13]

			scanning session, gives functional and anatomical pictures	techniques	
7	PACS	Chest TB, ovary, Breast tumor	Permanent storage of medical images	Expensive, require skilled technicians and use is complicate	[41]

CHAPTER 4: RESULT

Figure 4 represents the precise quantification of RNA-Sequence data derived from gene and isoform expression. According to the findings, practically all cancer tissues had higher amounts of BRCA1 and BRCA2 transcripts than their corresponding normal tissues did.

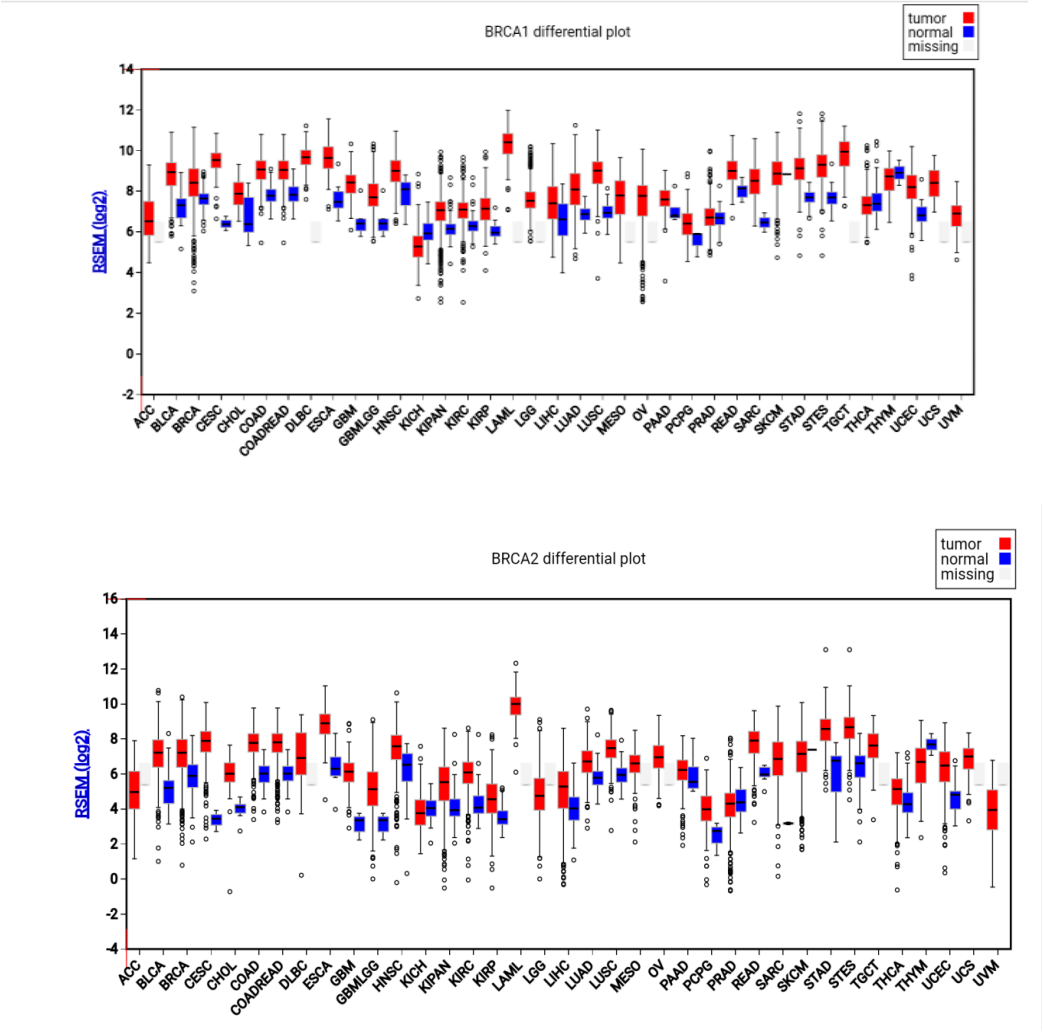
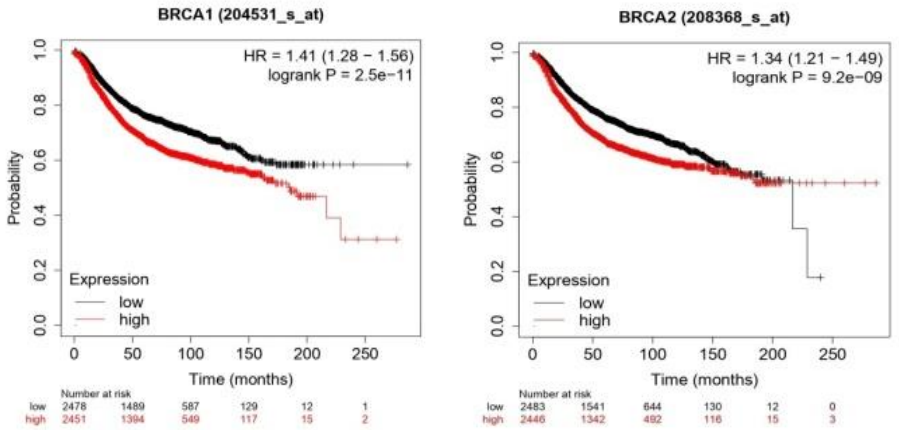
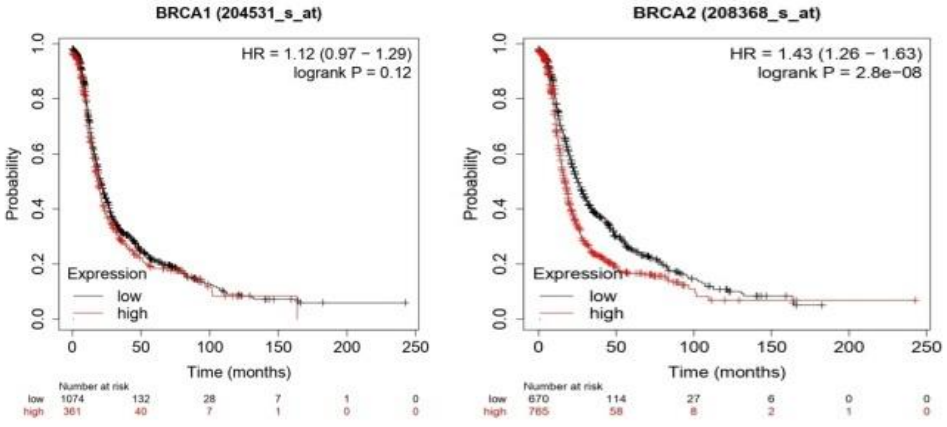


Figure 4: The generated boxplots displayed the target gene's level of expression, with red box denoting tumor samples and blue box denoting normal samples.Boxplots are a popular tool for comparing and visualising data distribution across many categories.In this study, the expression levels of the target gene in tumour samples and normal samples were compared. The median value is indicated by the line within the box. The difference in target gene expression levels among both categories can be seen visually by using red box for tumour sample and blue box for normal samples. Boxplots enable for rapid comparisons between categories and offer a succinct description of the data distribution.

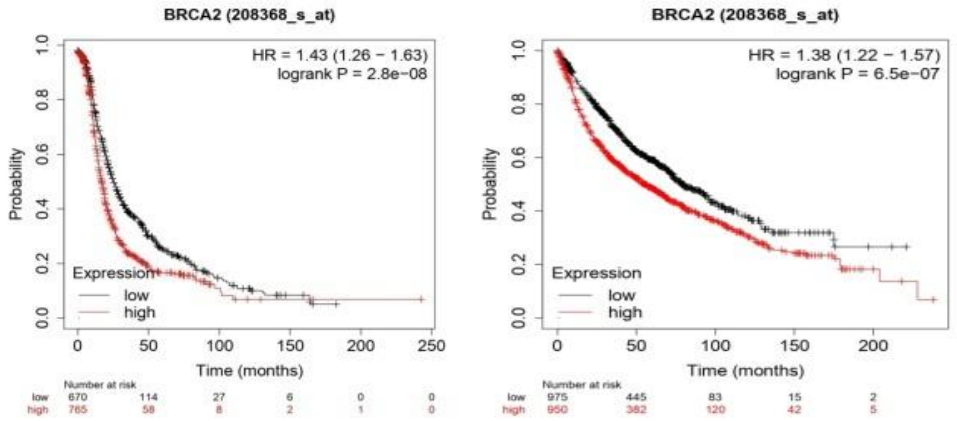
According to the findings of the KM study, high levels of BRCA1 expression were linked with a bad diagnosis for breast tumor suffering people (P=2.5e-11, Fig:2(A)), and high levels of BRCA2 expression were linked with a similar prognosis (P=9.2e-09, Fig:2(B)). There was no important correlation among the expression-levels of breast cancer 1 and endurance rate of the one suffering with ovarian tumor(P=0.12, Fig:2(C), while a higher level of Breast cancer 2 is linked along reduced survival rates of ovarian malignancy (P=2.8e-08, Fig. 2(D)). High levels of BRCA1 expression associated with a poor prognosis for lung cancer (P=2.8e-08, Fig: 2(E)) and elevated level of BRCA2 expression connected with similar prognosis (P=6.5e-07, Fig:2(F).



(A) (B)

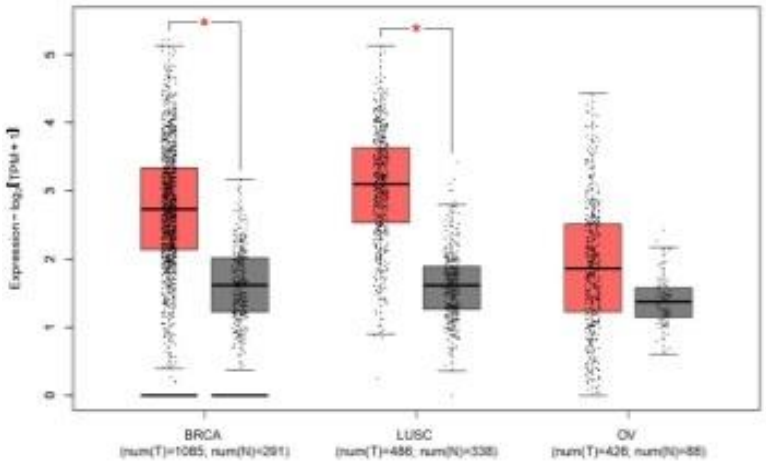


(C) (D)

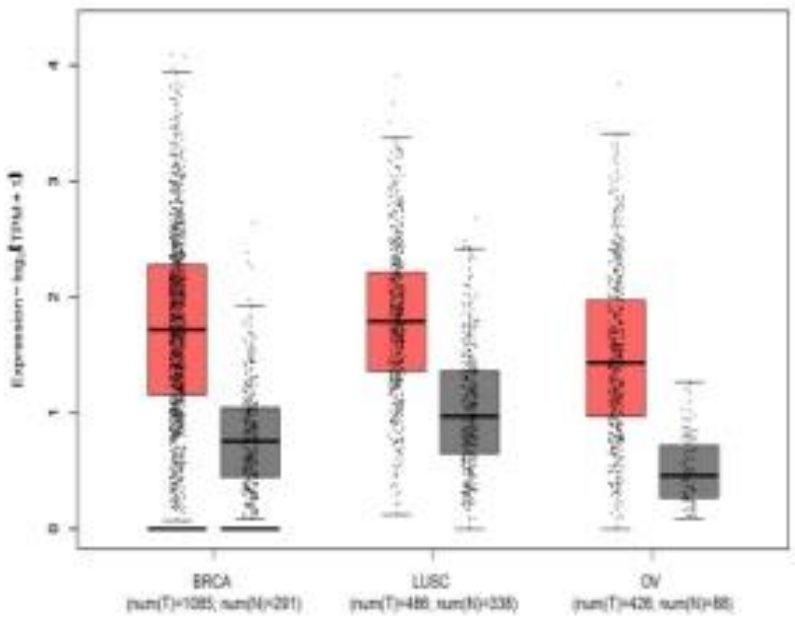


(E) (F)

Figure 5: A KM survival plot was used to display the overall survival-rate of patient with elevated and small levels of Breast cancer 1/2. High expression of Breast cancer 1 and Breast cancer 2 shown in red color and low expression shown in black color. HR is hazard ratio. Here it can be seen that expression levels of breast cancer gene (A) and (B), are negatively associated with the overall survival rate for breast tumor. (C) No major link amid the Breast tumor 1 expression level and the overall survival-rate of Ovarian tumor. (D) The amount of breast cancer 2 expressions is inversely correlated with the survival rate of ovarian tumor. In contrast, overall survival rate was negatively correlated in cases (E) and (F).



(A)



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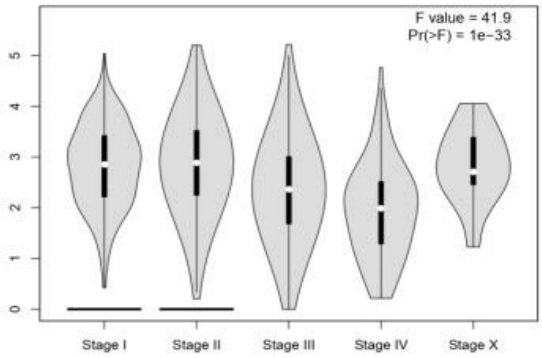
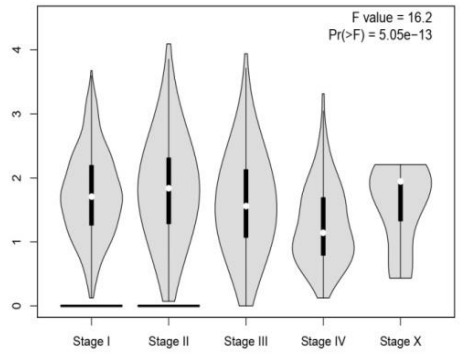


(C)



(D)

Figure 6: BRCA1 and BRCA2 gene expression data for BRCA, LUSC, OV obtained from the GEPIA2 database. (A) Box plots of the BRCA1 and (B) BRCA2 gene expression in BRCA, LUSC, OV with the black box representing normal samples and the red box representing tumor samples. (C) A pathological stage plot showing BRCA1 and (D) BRCA2 expression in the four tumor stages of BRCA, LUSC, OV

BRCA Protein Network

The BCRA1 and BCRA2 protein network contained genes with significant negative associations with key tumor suppressor genes as well as genes with high or very strong positive relationships with BCRA expression in the various malignancies. These proteins are all part of the same protein network, according to data from the STRING database and are involved in different pathways. By preferentially recognizing “Lys-63” linked ubiquitinated histones, at DNA lesions sites a component of complex BRCA1-A which is BABAM2 is able to drive heterodimer BRCA1-BARD1 at DNA damage site at DSB. UBE2K activates the formation of Lys-48 linked polyubiquitin chains in vitro, whether BRCA1-BARD1 E3 ubiquitin-protein ligase complex is present or not and is important with the homologous recombination repair pathway of double-stranded DNA break produced during DNA replication or triggered by DNA-damaging substances is the DNA repair protein RAD51B, also known as RAD51 homolog 2. This may encourage formation of RAD51 nucleoprotein filaments possesses DNA-dependent ATPase activity and binds single-stranded and double-stranded DNA. By attracting BRCA2 and RAD51 to DNA, PALB2, strongly encourages RAD51's ability to invade DNA strands. It stabilises the nucleoprotein filament against with the disruptive BRC3-BRC4 polypeptide, and helps RAD51 create D-loops via functionally collaborating with RAD51AP1 into the progress of the complex made by PALB2 linking BRCA1 and BRCA2. Cyclin-dependent kinase 2 is a STK protein kinase that regulates the cell cycle, phosphorylates BRCA2, causes DNA and centrosome duplication, promotes the E2F transcriptional programme and the start of DNA synthesis during the G1-S transition and controls G2 advancement.

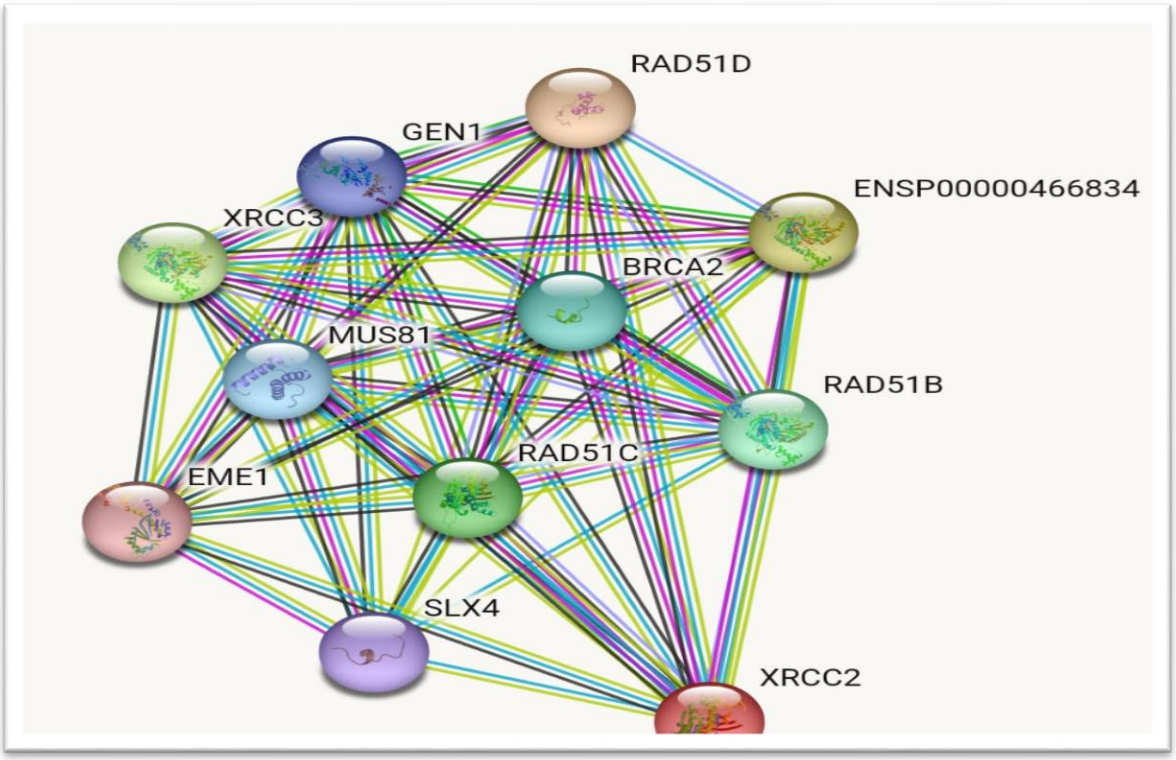


Figure 7: Protein Network analysis using STRING showing protein-protein interactions.

CHAPTER 5: CONCLUSION

BRCA1/BRCA2 tumor suppressor genes are the most studied genes of breast tumor and their heterozygous carrier shows loss of the gene's wild-type allele. They play a crucial part in activating DNA repair pathways in response to cellular stress. BRCA mutations occur frequently in breast cancer, but their prognostic impact on its outcomes have not been determined. Genetic instability is a result of the extremely high density of repetitive DNA elements in the BRCA1and BRCA2 genomic regions. In outbreaks of breast and ovarian cancer, promoter hypermethylation may silence the BRCA1 gene. Regular Sanger sequencing of exons as well as of the exon-intron junctions is used to screen the BRCA genes. Medical imaging informatics makes up a sizable portion of AI-based research-driven methods that has been approved by the Food and Drug Administration (FDA). These systems make use of machine- or deep-learning approaches to carry out a range of image analysis activities, including picture augmentation, segmentation, and abnormality identification as well as the prediction of the likelihood of malignancies. Among the most comprehensive standards for medical images is DICOM. It is designed to standardise picture data and make it simple to share between equipment from various manufacturers. Despite several glaring drawbacks, such as the need to include required data in picture headers, DICOM has proven to be a very full and, more importantly, useful standard for medical imaging preservation and exchanging.Artificial intelligence and machine learning are an interdisciplinary field that incorporates developments in computer science and neuroscience. The use of machine learning is now commonplace in a variety of industries, providing trustworthy assistance for decision-making and minimising human work. Contributions in AI-based medical imaging are still increasing rapidly. Despite these efforts, AI solutions are still just restricted solutions for particular conditions, imaging modalities, or disease states in the field of medical imaging.

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