ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2023; SP4: 85-90

Harsha Chopra
DPG Degree College, Gurugram, Haryana, India

Khyati Bhargava
DPG Degree College, Gurugram, Haryana, India

Indu Malik
DPG Degree College, Gurugram, Haryana, India

Correspondence Author;
Indu Malik
DPG Degree College, Gurugram, Haryana, India

(*Special Issue*)
"National Conference on Multidisciplinary research for sustainable development"

A review on microarray bioinformatics in cancer research

Harsha Chopra, Khyati Bhargava and Indu Malik

Abstract
The growth of information and technology over the last decade has been overwhelming, especially in the field and study of genomics. This was by far the most exciting thing for researchers to process experimental results. This was particularly because the traditional gene-by-gene approach was inadequate with regards to meeting the growing demand of researches in biology in an attempt to understand the true nature of biology. This has been recently made possible with the advent of Microarray Technology (MT) in which thousands of genes could be studied on a single glass slide without much of a hassle. The foregoing review article aims to throw light on this field as well as it's applicability in the field of oncology, different cancer researches and its potential diagnosis and cure. Microarray technology is the basis of this article, with particular focus on gene expression profiling of brain tumors and breast cancer.

Keywords: Bioinformatics, microarray, gene signature, gene expression profiling, brain tumors, breast cancer

1. Introduction
Bioinformatics is an emerging field of biological research which can be viewed as a combination of the use of engineering, statistical, computational and mathematical tools for the processing and analysis of biological data. As the name suggests, 'Bio' means related to life and 'Informatics' relating to computer applications and data storage. Thus, it is also known as 'Computational Biology'. Bioinformatics has mainly two main components which are (i) algorithm and software tools development and (ii) biological data interpretation and analysis using these particular algorithms and software tools [1]. The growth of information and technology over the last decade has been overwhelming, especially in the field and study of genomics. This was by far the most exciting thing for researchers to process experimental results. This was particularly because the traditional gene-by-gene approach was inadequate with regards to meeting the growing demand of researches in biology in an attempt to understand the true nature of biology. Considerable amount of data is generated by technologies such as DNA microarrays and genome sequencing. This makes it crucial to manage the data and its integration as well as storage for later use. This is done in a sequential manner by analysing the data, its interpretation for biological understanding and eventually utilizing it for therapeutic purposes. Researchers are shifting from laboratory atmosphere to 'virtual labs' or 'in-silico approach'. Because of this, traditional approaches are slowing switching to this bioinformatics era, making it the newest and emerging field of biology along with computer science, engineering, mathematics and statistics.

2. Microarray as a Bioinformatics Tool
Lots of genes and their products such as RNA and proteins work together in a complex network within the human body. The traditional gene-by-gene methodology is insufficient to create a global perspective of cellular function due to this intricacy and complexity.

The Microarray Technology (MT) was created to assess gene expression activity across the entire genome in a single experiment [2]. Base pairing property of DNA is exploited within this technology and thus the basic underlying principle is 'base pairing hybridisation'. When using a gene expression microarray, one collects the cells or tissue sample, purifies it and extracts the RNA by dissolving them in a mixture of various organic solvents. Other cellular components like DNA and proteins are separated leaving only RNA in the sample solution. After centrifugation of this sample, the supernatant is collected. This contains various RNAs including tRNA and rRNA which are not involved in gene expression. One needs to separate these and extract only the mRNA. This is done by passing the sample through a column containing beads having poly-T attached to them. mRNAs having poly-A tail hybridise with the poly-T sequence and other RNAs are discarded. Strands of mRNA attached to the beads having poly-T sequence by the poly-A tails are now contained in the column. To detach the mRNA from the beads, a buffer solution is passed over the column. The mRNA is then reverse transcribed to form the complementary DNA or cDNA and then fluorescently labelled to enable it to be detected under laser scanners. Once the cDNAs are hybridised to their complementary DNAs, or in other words, mRNAs to the DNAs it is transcribed from (ensured by sequence specific hybridisation), colour intensity for each gene is quantified using laser scanners and special analytical software which scan microarrays. These are further used for statistical analysis [3]. Summary of the experimental flow of microarray technology is depicted in Figure 1.

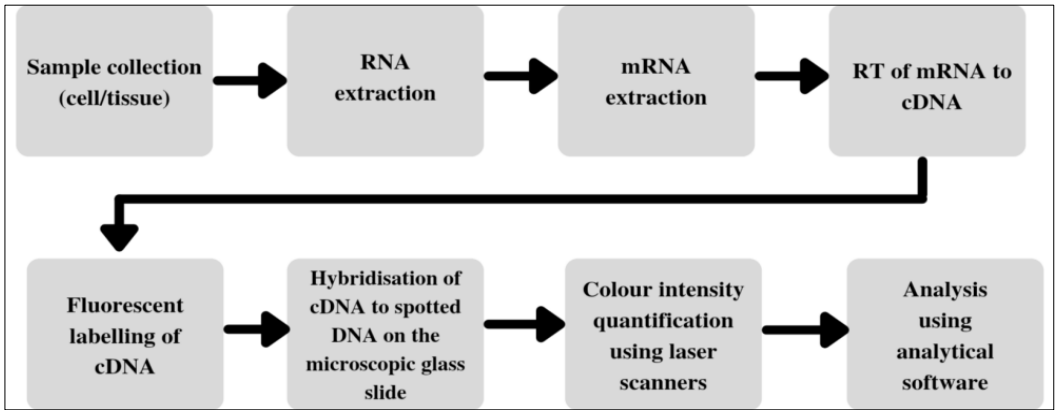

Fig 1: Summary of experimental flow of microarray technology

Now this experimental design could be optimized by subsequently taking normal tissue or cells as control and cancerous tissue or cells as sample. Cancer is a result of genetic mutation and is an example of "genes-gone-bad". Thus, detection of cancer through microarray technology can prove to be a milestone both in bioinformatics as well as biomedical sciences. Early detection would result in better treatment and reduced mortality rates due to it. Further, genetic abnormalities of different types and subtypes of cancers could be studied, recorded and analysed to check whether there are any similarities in the way genes mutate in a particular type of cancer. This can subsequently aid doctors and researchers to find a suitable prognosis for various patients.

3. Role of Microarray in Cancer Research

Microarray technology and data generated through it is most often used in cancer research, wherein early detection is critical in order to define the type of treatment and survivorship [4]. Microarray Technology enables researchers to examine the activity and expression of thousands of genes in a single experiment, thereby providing crucial information on the cell's function. This exact information can be used to diagnose a variety of diseases, including diabetes, Alzheimer's disease and various types of cancers [5].

Accumulation of genetic and epigenetic events results in the malignant transformation of cells. To study and understand its polymorphism and complexity, functional studies of cancer is important. It is obvious that technologies from the recently emerging fields such as genomics and proteomics would facilitate and aid in these investigations. Microarray technology is a revolutionary and effective method for extracting biomedical data that may be used in a variety of settings. It will offer high-throughput and relevant understanding on changes in a person's tumors relative to germline DNA, activity and expression of mRNA and protein within the field of cancer research. This comparison among individuals could provide a group of genes within a specific tissue, that are up or down regulated when contrasted with healthy controls, also called tissue-specific disease signatures. These signatures would be used to provide diagnosis on the basis of numerous informative genes. This could prove to be a revolutionary approach as the final outcome could most probably be a plethora of biomarkers which are both associated and specific to tumors that can aid in cancer aetiology, diagnostics, and treatments, eventually leading to cancer "molecular nosology" [6].

4. Gene Expression Analysis and Gene Profiling in Cancer using Data Obtained from Microarray Technology

All of the cells in an organism's body possess the exact same information contained in their genetic material, that is, DNA. Yet, only 3-5% of the genes are active in a particular cell at any given instance. This selective activation and regulation of the genome allows for a vast range of biological processes that are distinctive to each cell, as well as a variety of compensating reactions to environmental stresses. The majority of the genome is silent (selectively repressed), and regulation of gene expression is responsible for controlling this adaptive trait of all multicellular organisms. This regulation may occur at either transcriptional or translational level. Out of the two, most

regulations occur at transcriptional level since the expression of any protein is more efficient at this level. Hence, global analysis and assessment of gene expression might open the doors for an in-depth knowledge on cellular functions.

Transcript imaging, which was previously restricted to gene-by-gene strategies, was used to quantify gene expression. As a result, scientists have focused on approaches that permit large-scale investigations, using increasingly advanced molecular bio techniques to meet this requirement. The Human Genome Project benefits technologies like serial analysis of gene expression [7] and DNA microarrays by yielding a more comprehensive and annotated human genome.

By first producing tagged nucleic acid probes from genetic material in each sample, DNA microarrays allow broad-scale profiling of gene expression. It is worth mentioning that by computing the ratios of both signal intensities, gene profiling with DNA microarrays can offer the relative level of expression. This shows variations in the expression of the associated gene in the two samples that were compared quantitatively. As a result, the approach for dealing with the massive amount of expression data generated by microarray measurement is the next critical step through gene expression data analysis.

Scientists realised that simple analysis is a schism while examining data which contains thousands of genes on a single slide. Thus, gene expression analysis came into picture that brought together experts from various fields like statistics, mathematics and bioinformatics apart from biology. This consortium's aim was to construct effective bioinformatics tools which would then be able to analyse the gene expression data on a large scale with a greater efficiency. This was to be done by exploiting the full potential of microarrays and the data obtained as a result.

A thorough statistical study and analysis is crucial while mining data of express of genes with differential values. Thus, one method currently being used is "clustering" wherein samples or genes are grouped together on the basis of the similarities between them. This method evaluates each gene or sample as a mathematical component, computes the distance between them, and turns the results into a coefficient of correlation. In taxonomy and phylogenetic analyses, this idea is commonly applied. Further, supervised and unsupervised clustering are the two families of clustering technique as depicted in Figure 2. Both of these are widely used in the field of Bioinformatics.

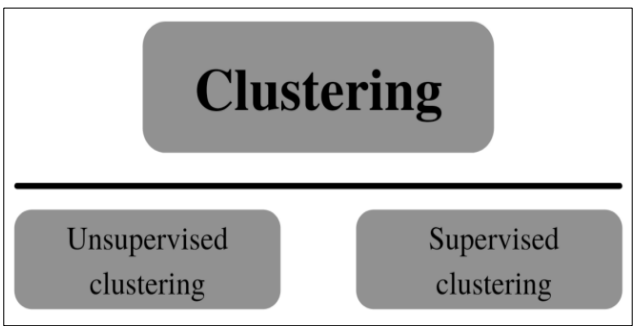

Fig 2: Classification of clustering technique for gene expression analysis

Unsupervised clustering does not make use of pre-existing data or previous knowledge regarding the genes which have already been analysed and stored in the form of databases and for which several algorithms have also been developed. Alternatively, supervised clustering implies previously known knowledge from references to understand the linkage or relation between genes or any sample for that matter. In a group of cancer patients with varying prognoses, for instance, a variety of diagnostic examinations and disease state variables could be utilised to influence clustering attainment. The generated gene profiles can subsequently be used to make worldwide diagnoses in the long term. The finding of class markers with varied topological properties is the primary objective of supervised clustering techniques. In pathological research, finding such molecular markers is becoming an intriguing and significant study focus. Analysis of gene expression usually starts with unsupervised clustering to organise the data before moving on to a supervised technique for precise clinical interpretations.

A spectrum of down or upregulated genes is revealed by microarray-based expression profiling, revealing a meaningful molecular fingerprint of the cellular environment and providing a massive network of prospective disease molecular markers. Global transcriptome analytics, when coupled with understanding of the medical impact of disease process, could have strong applicability in diagnosis of cancer and clinical care. The origin of human cancers, as well as their biochemical and genetic backgrounds, are diverse and unique to patients. [8] Variability in gene expression programmes across human cancers indicates these distinctions. Profiling disease-specific gene expression programmes could potentially offer a new foundation for human malignancy categorization. With the introduction of microarray technology, it became feasible to examine and comprehend cancer-specific gene expression patterns on a global rather than gene-by-gene basis.

Microarray technology is used in oncological studies for two primary reasons. To begin, it is necessary to comprehend the biology of specific cancer kinds or subtypes, their genetic mutations, and their abnormal biochemical mechanisms. This is essentially observational and microarray findings can be examined utilising pathways and gene annotations such as Gene Ontology. Furthermore, to categorise human cancers based on a specific parameter, such as organ type or subtype, patients prediction, therapy response prognosis, or metastatic origin. This could be accomplished in one of two distinct ways: (i) by focusing solely on the biology of a parameter; or (ii) by categorizing malignancies, in which the biology of the genes associated is less relevant than having accurate genes that can indicate the examined parameter [9, 10]. In attempt to discover accurate classifiers, these studies relate medical or biological information from tumors with their molecular profiles.

4.1 Gene Expression Profile for Brain Tumor

The histopathological characterization of brain tumor has largely led gene expression profiling. Brain tumors gene expression profiles were created in order to truly comprehend the biology and categorization of brain cancers (Table 1).

Table 1: Types of Brain Tumors

	Type of brain tumor	Characteristic features
Rpimary Tumors (Develop in the brain or surrounding cells, remain confined to the brain and CNS, categorised by the cell of origin)	Gliomas	Most common primary tumors; originate in glial/supportive cells
	Astrocytomas	Arise from star shaped astrocytes in brain or spinal cord; malignant
	Glioblastoma multiforme (GBM)/Glioblastoma	Aggressive and fast growing tumor; develop more commonly in frontal or temporal lobes of brain; malignant
	Meningioma/Meningeal tumors	Development from the membrane cells surrounding brain and spinal cord; mostly benign
	Ependymomas	Spinal cord tumor; occur in the ventricle linings or spaces in the brain around spinal cord; malignant
	Oligodendrogliomas	Occur in cerebrum from cells that produce myelin; very rare; malignant
	Mixed gliomas	Forms in cerebrum; have 2 types of cells (oligodendrocytes + astrocytes)
	Pituitary tumors	Found in pituitary gland; benign
	Medulloblastomas	Development in neurons of cerebellum; fast growing; malignant
	Primary CNS lymphomas	Development in brain's lymph tissues
Metastatic Tumors (begin or spread in other parts of the body)	Rhabdoid tumors	Spread throughout the CNS; very rare and aggressive; kidneys are the most common site for their appearance
	Acoustic neuromas	Types of schwannoma; arise from 8th cranial nerve and travels from brain to ear

Pomeroy and Scott [11] used biology to identify a gene signature that separated medulloblastomas from various histologically comparable brain tumors and this categorization could be used to determine clinical outcomes. This gene signature also demonstrated that medulloblastomas are fundamentally separate from primitive neuro-ectodermal tumors (PNETs), two forms of brain tumors that are commonly grouped together as a single entity. The medulloblastoma gene expression profile revealed an unanticipated activation of the Sonic Hedgehog signalling pathway and suggested cerebellar granule cells as the tumor's cell of genesis.

Bredel and colleagues [12] have also applied molecular networking learning to the identification of critical activities and processes linked with gliomagenesis, using gene expression profiling in the biological comprehension of human gliomas. Considering the transcription profiles of 50 human gliomas with diverse histologies, they discovered that the integrin signalling pathway is especially important in the glioblastoma subtype, which is recognized for its high invasive and metastatic nature. The MYC oncogene was also identified as a key networking component in the gliomagenesis mechanism. Three novel MYC-interacting genes with cancer-related functions, specifically UBE2C [1], EMP1 [2], and FBXW7 [3], as well as CD151 as a potential constituent of a system that regulates glioblastoma cell invasion, were discovered as networking components selectively activated in gliomas.

Pomeroy & Scott and Bredel with his colleagues have used biological methodologies to expand preexisting information about the organisational patterns of gene expression in human gliomas, allowing them to uncover possible novel targets towards eventual therapeutic advancements.

In brain tumors, identifying the biology is crucial, but categorization predicated on its interaction with therapeutic factors also provides useful insights Therapeutic attributes such as responsiveness to therapeutic medication, as well as histological subtype and gene mutations, can all be used to anticipate a patient's prognosis. French and Pim [13] identified a 16-gene signature which suggested oligodendroglioma clinical outcomes and a 103-gene signature that suggested survival outcomes. They have also been successful to identify gene signatures that differentiated oligodendrogliomas with 1p, 19q, or both chromosomal arms absent. Furthermore, Nutt and Catherine [14] identified a 20-gene signature that appears to determine the therapeutic prognosis of individuals with glioblastomas or high-grade oligodendrogliomas more effectively than traditional histological methods. They were also able to categorize high-grade gliomas with non-classical histology using this gene signature.

Collectively, these investigations on gene expression profiling have indicated that microarray technique could be useful in the molecular categorization of gliomas. This technique can help professionals in making more accurate diagnosis and treatment choices by improving the identification of tumor subgroups and the connection of clinical factors. The breakthroughs by French and Pim that gene expression profiles represent not just the biology and clinical behaviour of gliomas, but also its core molecular underpinnings, seem to be the most remarkable. Glioma subtypes are distinguished by their clinical and histological features; even so, molecular profiles relying on the underlying transcripts could further identify subtypes. These molecular profiles are especially relevant for individuals with brain tumors who are in desperate need of newer therapy options.

4.2 Gene Expression Profile for Breast Cancer

The very first people to investigate the science of human cancers using their own gene expression programme by employing microarray technique were Perou and Botstein. [15] Relying on the profiles of gene expression which coincided with already reported histopathological expression profiles of proteins, they were successful in classifying numerous breast cancer subtypes. Genes whose variable expression patterns may be linked to distinct histological characteristics of breast cancers were classified as ‘intrinsic' gene signatures. Sorlie and colleagues updated their intrinsic gene signatures in a succession of follow-up articles, linking 5 molecular subtypes of breast cancer (Table 2) to patient survival statistics. These researchers' five subtypes highlight the fundamental biology of the cell which determines the clustered subdivision of subtypes of breast cancer.

[1] A gene which codes for Ubiquitin-conjugating enzyme E2 C protein

[2] Epithelium membrane protein 1 encoding gene

[3] F-Box and WD Repeat Domain Containing 7- a tumor suppressor gene

Table 2: Breast cancer molecular subtypes

S. No	Cancer subtypes	Characteristics
1.	Luminal A breast cancer	Express ER [4]; linked to healthy prognosis
2.	Luminal B breast cancer	Express ER; linked to less healthy prognosis
3.	ERBB2 [5]	Overexpress ERBB2; mostly ER negative; poor prognosis
4.	Basal-like	Express basal cytokeratins, laminin and integrin; ER, PR5 [6] and ERBB2 absent; aggressive clinical activity
5.	Normal-like	Express genes that are expressed in non-epithelial cells or adipose tissues; basal epithelial gene expression- high and luminal epithelial gene expression- low.

These tumors similarly showed high basal epithelial gene expression and minimal luminal epithelial gene expression. Certain recognised cancer genes, namely TP53 [7], BRCA1 [8] and EGFR [9], have also been linked to molecular profiles. The root alteration is thought to be causing the segregation of the samples in such research. Other significant advances pertaining to the use microarrays involving gene expression profiles for researches on breast cancer include it's categorization based on patient medical outcomes. Van't Veer and associates [16] was the first one to identify a 70-gene expression signature that indicated metastases which don't spread to the lymphatic system primarily the lymph nodes in and around the breast cancer site. These are known as "lymph node negative breast cancer". Such patients were reported before the age of 55. In lymphatic node negative breast cancer individuals having estrogen receptors who underwent hormone therapies containing adjuvants, a 21 gene expression signature was demonstrated to indicate metastases [17]. Regardless of age or ER condition, a 76-gene expression signature indicated metastases in lymphatic node-negative women with breast cancer who would not have taken any adjuvant medication treatment [18]. Lastly, a 44-gene signature has been found to indicate breast cancer reactivity to Tamoxifen therapy more accurately than the tumor's ER state [19]. Microarray technology's potential to detect breast cancer individuals with a better or worse prognosis for developing metastasis should assist physicians decide whether to skip adjuvant medication treatment or pursue more intensive therapy choices. It may also be beneficial in predicting the region of metastasis, as evidenced by a published study of breast cancers that metastasized to the bones [20].

5. Recent Applications in the Field of Oncology

Microarrays are employed in cancer study to explore diagnoses, cancer development and variability in systemic treatment. The morphological form of the tumors was used to classify cancers in the past, however this has major limits since histology is inadequate to determine progression of the disease and clinical prognosis. To address this, a number of researcher organisations have attempted to use the Microarray Technique as depicted in Table 3, in order to discover subgroups of cancer that are pathologically specific that could be used to estimate patient survival and therapeutic effectiveness. Expanding knowledge and conceptual understanding of gene functioning is a common goal of microarray investigations with research objectives [21]. This is commonly accomplished by looking at genes whose expression patterns are linked to specific experimental situations or phenotypes. This could include identifying biological pathways influenced by a gene's expression patterns as well as features of drug targets and drug sensitivity in the formulation of therapeutics.

Table 3: Applications of Microarray and related technologies in Oncology

S. No	Technology	Application
1.	Software Omni-*Viz* SAM [10]	Identify AML [11] subgroups
2.	PAM [12]	To find predictive gene clusters for AML, class predictors were identified.
3.	These approaches are combined in unusual ways	Combinations could better determine survival rates in AML patients, even those with a neutral karyotype

Secondly, microarray investigations could also be used to answer issues about a disease's phenotype. These researches are aimed at figuring out which biological pathways are linked to various characteristics or subtypes of condition, as well as identifying molecular markers that are specific to the particular disease. This kind of data could be extremely useful to decipher the complicated molecular pathways at work in a disease.

Microarray investigation in a further approach is motivated by patient-related research issues. Responses to such queries may help in disease diagnosis and therapy. Microarrays are particularly valuable in prognosis since they can forecast future occurrences that aren't yet clinically observable by measuring gene expression levels (like cancer metastasis) [22].

Researchers have recently used various computer algorithms to help in cancer diagnosis by looking at the some extremely relevant genes. Gene selection is a tool for identifying the most relevant genes that can improve diagnosis of the disease and prediction precision.

6. Conclusion

As malignancies originate from the aggregation of various genetic and epigenetic alterations, microarray techniques are becoming much more essential in oncology. Microarrays are progressively being utilised to classify cancers for medical diagnostics. In cancer research, extensive and high-throughput genomic analysis is an unavoidable research instrument.

But, there still are significant disadvantages to using microarrays on a regular basis. Microarray assays are expensive, and experimental processes must be more reliable. Microarray and experiment procedure standardisation is also necessary for examining data from different academic researchers. Equipment and methodologies for statistical analysis must also be devised. Even after such drawbacks, it is apparent that microarray technique will become a standard approach in cancer future studies. Timely cancer detection will be done with

[4] Estrogen receptor
[5] Also called HER2 for Human Epidermal Growth Factor Receptor
[6] Progesterone receptor
[7] Tumor protein 53 encoding gene- a tumor suppressor
[8] Breast cancer type 1 susceptibility protein encoding gene
[9] Epidermal growth factor receptor encoding gene
[10] Significant Analysis of Microarrays, developed by Stanford
[11] Acute Myeloid Leukemia
[12] Prediction Analysis for Microarrays

oligonucleotide microarray analysis, and gene expression profiles would be used to determine prognosis after chemotherapy or radiation therapy. Gene expression assessment employing microarrays, combined with traditional histopathology data, will aid investigators in finding meaningful solutions to cancer-related problems. Microarray technology will be refined further with the use of advanced bioinformatics tools.

The fusion of robotic systems, bioinformatics, and programming, and the accomplishment of various sequencing projects of the complete genome for numerous species, has culminated in significant advancements in biology and medicine. Biological investigators have typically looked at functional genetic data to understand underlying cellular processes and the causes of clinical diseases. Researchers are immersed in data in today's post-genome age, attempting to govern high-throughput systems of experiments and grasp the myriad of interrelationships between small molecules, phenotype and proteins. On a single glass slide, highly dense arrays of defined DNA sequences that comprise each identified gene of a species may now be generated. In the fundamental life sciences, along with diagnoses and therapies in the healthcare arena, genomics, bioinformatics, and automation would play an extremely essential function as discovery tools. Numerous instruments are constantly being created in the microarray domain, both in terms of technologies and analytics, and the potential to integrate these innovations to a wide range of biological disciplines is incredible. Researchers are becoming much more conscious of the possibilities of microarrays to advance their study, and as science advances, so does understanding of and prospective remedies to the constraints that microarrays may still have.

7. References

1. Zhang, Zhaojun, *et al.* Bioinformatics; c2009.
2. Neagu, Monica, Marinela Bostan, Carolina Constantin. "Protein microarray technology: Assisting personalized medicine in oncology. World Academy of Sciences Journal. 2019;1.3:113-124.
3. Ewis, Ashraf A, *et al*. A history of microarrays in biomedicine. Expert review of molecular diagnostics. 2005;5.3:315-328.
4. Selvaraj, Saravanakumar, Jeyakumar Natarajan. Microarray data analysis and mining tools. Bio information. 2011;6.3:95.
5. Hambali, Moshood A, Tinuke O Oladele, Kayode S Adewole. Microarray cancer feature selection: Review, challenges and research directions. International Journal of Cognitive Computing in Engineering; c2020.
6. Mohr, Steve, *et al*. Microarrays as cancer keys: an array of possibilities. Journal of Clinical Oncology. 2002;20.14:3165-3175.
7. Velculescu, Victor E, *et al*. Serial analysis of gene expression. Science. 1995;270.5235:484-487.
8. Marquard, Andrea Marion, *et al*. Tumor Tracer: A method to identify the tissue of origin from the somatic mutations of a tumor specimen. BMC Medical Genomics. 2015;8.1:1-13.
9. Wang, Yixin, *et al*. Gene expression profiles and prognostic markers for primary breast cancer. Microarray Data Analysis; c2007. p. 131-138.
10. Chang, Jenny C, *et al*. Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. The Lancet 362.9381; c2003. p. 362-369.
11. Pomeroy, Scott L, *et al*. Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature. 415.6870; c2002. p. 436-442.
12. Bredel, Markus, *et al*. Functional network analysis reveals extended gliomagenesis pathway maps and three novel MYC-interacting genes in human gliomas. Cancer research. c2005;65.19:8679-8689.
13. French, Pim J, *et al*. Gene expression profiles associated with treatment response in oligodend-roglioma. Cancer research. 2005;65.24:11335-11344.
14. Nutt Catherine L, *et al*. Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. Cancer research. 2003;63.7:1602-1607.
15. Perou, Charles M, *et al*. Molecular portraits of human breast tumours. Nature. 2000;406.6797:747-752.
16. Ko, Jae-Hong, *et al*. Expression profiling of ion channel genes predicts clinical outcome in breast cancer." Molecular Cancer. 2013;12.1:1-17.
17. Van't Veer, Laura J, Soonmyung Paik, Daniel F Hayes. Gene expression profiling of breast cancer: A new tumor marker. Journal of Clinical Oncology. 2005;23.8:1631-1635.
18. Smid Marcel, *et al*. Genes associated with breast cancer metastatic to bone. Journal of Clinical Oncology. 2006;24.15:2261-2267.
19. Jansen, Maurice PHM, *et al*. Molecular classification of tamoxifen-resistant breast carcinomas by gene expression profiling. Journal of clinical oncology. c2005;23.4:732-740.
20. Tao, Ziqi, *et al*. Microarray bioinformatics in cancer-a review. J buon. 2017;22:838-843.
21. Hu, Nan, *et al*. Integrative genomics analysis of genes with biallelic loss and its relation to the expression of mRNA and micro-RNA in esophageal squamous cell carcinoma. BMC genomics. 2015;16.1:1-11.
22. Kaifi, Jussuf T, *et al*. Circulating tumor cell isolation during resection of colorectal cancer lung and liver metastases: A prospective trial with different detection techniques. Cancer biology & therapy. 2015;16.5:699-708.