ISSN 2816-8089

REVIEW ARTICLE

Review of Bioinformatics Tools and Techniques to Accelerate Ovarian Cancer Research

Anam Beg[1]* and Rafat Parveen[1]

[1]*Department of Computer Science, Jamia Millia Islamia, New Delhi 110025, India.*

Abstract

Since the history of humans there was no definitive cure for cancer. The rapid development in the field of bioinformatics has resulted in acceleration of advancement of cancer research. As computing and IT technology improves over time the use and importance of bioinformatics will also rise. The bulk of biological data created by biomedical researchers has increased over the years, and it has become difficult to store and analyze that data. Faster computer processors and advancement in quantum computing will solve the conventional problem of slow data processing and will make the use of bioinformatics even attractive for scientists and researchers across the globe. The success of potential drug candidates and vaccines were identified, and credit goes to bioinformatics gene simulation sequencing, simulation and fast data processing. The results were development of a vaccine in record time all thanks to bioinformatics approaches. This paper explores the contribution that bioinformatics has been able to make in the field of ovarian cancer and how the use of DNA sequencing and simulation helped in developing targeted drugs such as PARP inhibitors. It also elucidates the impact bioinformatics can make in developing effective therapies in times to come. Genome sequencing has paved the way in understanding the disease, possible treatment options analyze mutations and further predict the drug target. In this review we will highlight different aspects of bioinformatics tools and techniques that have accelerated the ovarian cancer research.

Key Words: *Bioinformatics; Ovarian cancer research; Drug discovery*

Corresponding Author: *Anam Beg, Research Scholar, Department of Computer Science, Jamia Millia Islamia, New Delhi-110025, India; E-mail: anamrazabeg@gmail.com*

***Received Date**: August 19, 2021, **Accepted Date**: October 25, 2021, **Published Date**: December 31, 2021*

***Citation**: Anam Beg and Rafat Parveen. Review of Bioinformatics Tools and Techniques to Accelerate Ovarian Cancer Research. Int J Bioinfor Intell Comput. 2022;1(1):01-10.*

1. Introduction

The deadliest form of cancer among women is ovarian cancer and it is placed 4th among all the fatal diseases. Due to the heterogeneous nature of ovarian carcinoma, the advancement in disease crosses several molecular levels. Basically, ovaries have three major sites where the tumor grows. Among them, the majority of malignancy developed from surface epithelium, serous ovarian develops at old stage and is the most common. The young stage carcinoma is called endometrioid carcinoma and is associated with endometriosis and is of third type. Germs cells and stroma are some other areas where ovarian cancer is developed. The survival rate with these diseases is only 45.6% *i.e.*, 5years of life expectancy. Also, if early-stage detection is feasible the survival rate increases up to 70%. Due to the absence of peritoneal covering in ovaries the cancer spreads locally to the peritoneal cavity as a result of which the healthcare professionals get confused between ovarian cancer and other gynecologic diseases that result in late detection. The present diagnostic and detection tools are not efficient for screening of ovarian cancer.

The most extensively used biomarker is carbohydrate antigen-125 (CA-125) but it shows elevations when 50% of ovarian cancer is already expressed. HE4 (Human epididymis protein 4) is also a biomarker for ovarian cancer having greater specificity and a less sensitivity than CA-125. Although many biomarkers have been studied, still major challenges are poor sensitivity and lack of specificity. A combination of transvaginal ultrasound and CA125 are required for better screening. Hence the use of bioinformatics approaches successfully found some new biomarkers with high specificity and sensitivity for the diagnosis of different types of cancer.

During tumorigenesis, to get genetic alteration microarray technology has been broadly used. To process the data generated by microarray, bioinformatics is extensively used. At present several bioinformatics approaches are extensively used to find the targeted drugs and potential genes and pathways responsible for ovarian cancer. Hub genes screening and to find associated drugs for ovarian cancer integrated bioinformatics analysis is being performed to understand the molecular mechanism behind tumorigenesis and prognosis of ovarian cancer. Further we will be discussing some bioinformatics advancement in ovarian cancer being done so far. Figure 1 represents different approaches of bioinformatics being used in ovarian cancer.

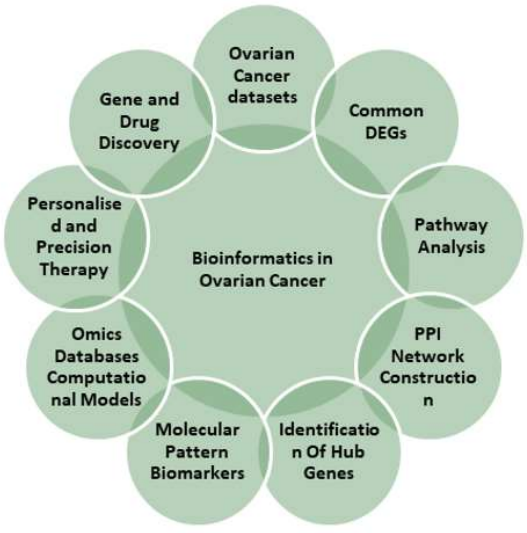

Figure 1: *Application and assets of bioinformatics in ovarian cancer.*

2. Cancer Research *via* Bioinformatics

Cancer irrespective of type and nature is one of the most feared diseases in the world today. It is not only difficult and, in some cases, even impossible to cure but can also be difficult to diagnose. Its early diagnosis, prognosis, and classification to a subtype have become necessary as it facilitates the subsequent clinical management and therapeutics plan. Computational Intelligence (CI) methods, including artificial neural networks (ANNs), fuzzy logic, evolutionary computations, various machine learning and deep learning and nature-inspired algorithms (ACO, Firefly algorithm, PSO, Bat algorithm, Bacterial foraging, BeeHive, Cuckoo search, *etc*), have been widely utilized in various aspects of oncology research *viz*. diagnosis, prognosis, therapeutics and optimized clinical management. Most cancers stay undetected and patients only show symptoms when the disease progresses. This leads to difficulty in treating the disease and is mostly difficult for the patient as chemotherapy has many side effects; hence early diagnosis plays a crucial role in disease management.

Bioinformatics and Computational Intelligence methods in the field of computational oncology, especially cancer diagnosis, prognosis and its optimized therapeutics have made appreciable progress towards understanding the hallmarks of cancer development, progression, and its effective therapeutics. However, extrinsic, and intrinsic factors which lead to drastic increment in incidence cases, the detection, diagnosis, prognosis, and therapeutics remains an apex challenge for the medical fraternity. With the advent in Computational Intelligence -based approaches, including nature-inspired techniques, and availability of clinical data from various high-throughput experiments, medical consultants, researchers, and oncologists have seen a hope to devise and employ Computational Intelligence in various aspects of oncology.

The development contributed by bioinformatics in cancer research since past many years are mentioned below.

2.1. Microarray experiments

The biggest milestone that was achieved in 1995, was the development of microarray. Since then, microarrays have revolutionized genetics research and DNA chip technology. Thousands of mRNA transcripts can be measured in the single experiment with the help of Gene-expression profiling using DNA microarrays. Monitoring of gene expression in case of acute leukemia was being done by DNA microarray to produce a classifier that could distinguish AML (acute myeloid leukemia) and ALL (acute lymphoblastic leukemia). Since then, number of gene expression signatures have been developed and used to classify different tumor types, recognize different stages of tumors as well as predict the prognosis of the diseases [1]. Bernards et al in 2002 first developed and validated the 70-gene signature in 295 patients with breast cancer. MammaPrint test is the first 'prognostic gene signature', which has been given approval by FDA and is being used in various studies. Microarray based gene expression profiling in breast cancer sets an example for ovarian cancer and for every other gynecological malignancy. The development of gene expression profiling based on microarray leads to major advancement in ovarian cancer classification, prognostication and prediction. After the process of microarray experiment a lot of data is being generated that need to be stored in various repositories and these are Stanford Microarray databases (SMD),

GEO (NCI gene expression omnibus); and for the biological interpretation the annotation databases are used which are KEGG, GO, GenMAPP [1].

2.2. Bioinformatics techniques

2.2.1. Genome editing tools

Any changes in DNA (deletion, duplication, mutation etc.) leads to cancer; ever since scientists realized the fact, they were searching to correct those changes *via* gene editing, but nothing fits easily. In 2013 a breakthrough was achieved called CRISPR; the alteration in human DNA can be made *via* this gene editing tool with the help of bioinformatics. It has shifted the line in the research world between possible and impossible. CRISPR is more precise that any other DNA-editing tool and can edit any segment of DNA within the 3 billion letters of the human genome. As of today, a number of genome engineering tools are available and their comparisons are being done Guha.et.al. But strategies are still being made to avoid toxicity and increase specificity issues that arise due to off-target activities and attempts are now being made to provide temporal control over the DNA-cutting activities of genome editing tools. In ovarian cancer CRISPR is being used to induce mutation into genes [2].

2.2.2. EBImage and RNA splicing

With the help of specific markers imaging cells are analyzed to localize cellular structure and proteins. Analysis of images and multidimensional processing are provided with the help of EBImage [3]. In recent studies machine learning approaches are being made to distinguish tumor phenotypes by combining digital pathology along with transcriptome analysis in majority of ovarian cancer [4]. The splicing of RNA plays an important role in cancer research. The diversity of protein function is found to be increased by alternative splicing if pre-RNA. In the process of splicing a part of a gene is either included or excluded to produce protein isoforms; the resulting isoform have different functions and it plays an important role in early carcinogenesis. For the early detection of cancer these cancer specific proteins serve as potential biomarkers [5]. Researchers showed that downregulation of FOX2 expression in ovarian cancer; and its splicing is altered in breast cancer samples [6]. Numerous studies have concluded that tumor development is correlated with alternative splicing, and further revealed that these many splicing networks could be used as potential predictor and therapeutic targets in ovarian cancer patients [7,8]. CI, CNN methods are also used for cancer image analysis.

2.3. Bioinformatics in cancer immunology

Results from preclinical studies have shown the interaction between tumor and immune system (Charoentong, Angelova et al. 2012); moreover, in tumor pathogenesis and progression immunity plays a crucial role (Charoentong, Angelova et al. 2012). With the help of bioinformatics in cancer immunology many tools and technique are being developed for epitope prediction tool, network modeling and integrative data analysis; moreover, technique have been developed for the analysis of next generation sequencing data but having meaningful biological results, still remain a challenge, hence different pipelines are introduced to overcome these issues. Different software tools are used to analyze all steps starting from raw sequences to a set of final annotations, *e.g.,* HugeSeq [9], Treat [10] SIMPLEX [11], *etc.* In ovarian cancer immunotherapy has shown tremendous potential in addressing the disease and various clinical trials are still underway for new treatments. These are the class of

treatments that take advantage of patients' own immune system to kill cancer cells. FDA has approved one immunotherapy option for ovarian cancer *i.e.*, Bevacizumab (Avastin®) is a monoclonal antibody that inhibits tumor growth by targeting VEGF/VEGFR pathway. It is approved for patients with relapsed ovarian cancer and newly diagnosed patients with ovarian cancer. Hence many approaches are being used in combination with immunotherapy to treat the disease [12].

2.4. Drug development and cancer vaccines

2.4.1. Small molecule inhibitors

In ovarian cancer small molecule inhibitors have shown to have promising results. The traditional methods of cancer therapy and drug targets have now been turned to the use of small molecule inhibitors like proteasomes, matrix heat shock proteins, metalloproteinases, different kinases *viz*; serine, threonine, tyrosine etc. These small molecular targets act as a selective eliminator of target cells. With high structural diversity these small molecule inhibitors lead to the success of potential drug targets responsible for chemotherapy in various cancers. The only computational approach available is Virtual screening which is cost effective. This technique assisted in identifying potential drug targets in various kinases CAMK4 [13], MARK4 [14]. In case of ovarian cancer an orally active novel small molecule (gp130 inhibitor) was discovered for the treatment of OC [15]. Similarly, many active compounds (small molecule inhibitor) have been found which down regulates the ovarian cancer cell proliferation, invasion and tumor angiogenesis [16]. Furthermore, novel small molecule inhibitor has been identified with the help of in silico screening that counteracts PARP inhibitor resistance in ovarian cancer [17]. Studies suggested that the proliferation of ovarian cancer cells are inhibited by the small molecule inhibitor TL4 [18].

2.4.2. Cancer vaccines

The science that is based on bioinformatics acquisition for the investigation of biological data for humans' immunology and disease agents are called vaccine informatics. (Raman et al., 2014). To study cancer vaccines many computational approaches and experimental validations are applied. Cancer vaccines are of many types' *e.g.*, epigenetic vaccines, genetic vaccines, peptide protein vaccines and cell-based vaccines. Long term immunologic memory is being provided by vaccine-induced immune response. The vaccination *e.g.*, **Vacuum** [19] is helpful in cancer therapy and is made up of peptides. The TP53 gene is usually mutated in ovarian cancer which encodes the tumor suppressor p53. Intratumoral T cell responses have shown by eight most commonly mutated positions of p53 in recent studies [20]. But still the immunogenicity in ovarian cancer is ambiguous. In the near future we might need multiple immunotherapies to provoke immune responses in patients with ovarian cancer. Sustained immune responses are shown by peptide vaccines (which are cost effective as well) in comparison to synthetic drugs.

2.5. Cancer screening and prevention at an early stage

2.5.1. Genetic testing

With the increasing advancement in genome sequencing and different technologies doctors around the globe are recommending genetic testing for women who are either carrying a family history of breast/ovarian cancer, multiple myeloma or leukemia. BRCA1 and BRCA2

are two most common genes associated with breast/ovarian cancer in women [21]. BRCA1 mutations in men are at a higher lifetime risk of getting prostate cancer & male breast cancer [22]. Mutation in any of the key genes might lead to increased chances of getting cancer. Any alteration in genes or the mutated segment of DNA is being looked after by genetic tests. Today customizations of cancer treatment are being done by genetic testing *e.g*., Oncotype DX™ assay is given to patients with positive breast cancer where chemotherapy is not required [23]. A team of clinical investigators, biostaticians and biological scientists validates these genomic tests. Patients carrying BRCA mutation in ovarian cancer respond better to Platinum rather than hormonal therapy [24]. In BRCA positive women's drugs like Olaparib have been found to be more effective than any other course of treatment [25]. Hence genetic testing has helped individuals in not only preparing for possible health conditions but also focusing on financial, career and even family planning.

2.5.2. SELDI-TOF MS + Bioinformatics tools

In 2004 for early-stage detection of different cancer types SELDI-TOF MS along with Protein Chip technology was developed [26,27]. Scientist found some new biomarkers when SELDI-TOF MS is coupled with bioinformatics approach [28] and achieved high sensitivity and specificity for the diagnosis of prostate, breast, colorectal cancer, liver cancer and so on. After studies showed that the pattern of SELDI 3 biomarkers was able to diagnose early-stage ovarian cancer with 74% sensitivity at 97% specificity [29]

2.6. Recent advancement in ovarian cancer- Bioinformatics approaches

Besides above-mentioned methods there are many other recent developments which are widely appreciated for the diagnosis, prognosis, and optimization of therapeutics of various cancers. For example, Fuzzy logic in cancer prediction, cancer risk analysis, decision support systems, tumor detection and grading in MRI/CT/other radiological images; Evolutionary algorithms (GA, GP, CGP, GEP) for cancer detection, diagnosis, prognosis, gene biomarker identification, *etc*. The methods based on Computational intelligence are helpful for early diagnosis of cancer and predicting its susceptibility from SNP data. Computational intelligence methods are also helpful for cancer recurrence prediction and in clinical decision support systems. bioinformatics advancement has the pay for the development of different tools/technique to find novel genes, drug targets and pathways involved in ovarian cancer [30]. Moreover, many studies have concluded the role of potential tumor suppressor genes and find potential drug targets against them [31,32]. Apart from Computational intelligence, Machine learning based models are also effective in cancer therapeutics. Computational intelligence together with artificial intelligence plays an important role in precision therapies and cancer surveillance. Last but not the least bioinformatics advancement in Machine learning helps in integrative gene network construction to analyze cancer, predict drug response and together with deep learning it boosts anticancer drug development [33]

Thousands of mRNA transcripts can be measured in the single experiment with the help of Gene-expression profiling using DNA microarrays. Results from such studies confirmed that cancers are not a single disease instead it's a group of molecularly distinct neoplastic disorders. Besides these Gene Expression Signatures are also used in De novo generation of hit-like molecules using artificial intelligence; recently a research article from neuroscience have concluded that a dopamine-induced gene expression signature regulates neuronal function and cocaine response**.** Furthermore, Gene expression analyses are used in the identification of potential gene signatures that serve as potent biomarkers in ovarian cancer

and are responsible for the vulnerability to develop complicated disease. Apart from all these continuous progresses has been made in the field of deep learning, machine learning and numerous bioinformatics tools and techniques are developed to hasten the gene expression, identification of gene biomarkers, finding prognostic genes etc. in various other diseases. For instance, a machine learning model called GVES [34] is used for the identification of prognostic genes with small data set. Similarly, HE2RNA [35], a model based on the integration of multiple data modes is used to predict RNA-seq expression of tumors from whole slide images. In case of ovarian cancer Cox Proportional Hazard regression models are employed to identify gene expression patterns associated with disease mortality and progression. For the interpretation of genomic signatures GATHER [36] tool is used and for the simplification of gene expression signature analysis a web-based resource called SIGNATURE [37], have been developed which provides software, data, and protocols to perform the analysis successfully. Hence efforts are being made to understand the mechanism behind molecular signatures which could help us anticipate the potency of ovarian cancer. Many biomarkers have already been studied and many are underway to know the onset of Ovarian Cancer: for example, the deregulation in tumor suppressor genes, miRNAs and epigenetics.

With the increasing cause of death among women due to ovarian cancer, many techniques are implicated to find the differentially expressed genes that are responsible for early prognosis and development in ovarian cancer. It is also revealed that microRNAs regulate gene expression in tumors by interacting with mRNAs [38]. Although the research regarding OC and microRNAs is extensive but still many miRNAs are being found which plays pivotal role in causing early development in ovarian cancer. Recent research has shown that MIR502, which is regulated by NRF1, acts as a tumor suppressor gene to accelerate apoptosis and suppress proliferation by targeting the Hippo signaling pathway in ovarian cancer (Yan Li, Article number: 77 (2020)). Similarly, up-regulation of miR-141 and down-regulation of miR-205 and miR-125b have a central role in transforming endometriosis to ovarian cancer [39]. Various omics analysis is being employed to identify key biomarkers in ovarian cancer. Hence the role of bioinformatics has been highlighted in Drug Discovery Development, proteomics, genetics, modeling, miRNA discovery and assessment, and clinical genome sequencing. By association, bioinformatics and pharmacovigilance promoted both sample analyzes and interpretation of drug side effects, also focusing on drug discovery and development (DDD), in which systems biology, a personalized approach, and drug repositioning were considered together with translational medicine [40].

3. Conclusion

Globally OC ranks fifth among various gynecological diseases which lead to death. The baseline prognosis and tumorigenesis are still not understood. In case of ovarian cancer, it is more important to diagnose the disease early as most women don't show any symptoms till the disease reaches an advanced stage and also when a patient does show symptoms the symptoms may be vague and the physician may fail to correlate the clinical symptoms leading to losing precious time. Patients with beginning OC have a curing rate of 90% but only 20% of Ovarian Cancer are detected at stage1. Irrespective of many tools and techniques being developed for different cancer types (Immunotherapy, targeted therapy hormonal therapy, inhibitors, modulators and cancer vaccines), OC is still the deadliest malignancy among women. It is therefore a dire need of an hour to find biomarkers that are more specific and sensitive at an initial stage. And for this we need bioinformatics approaches to solve the problem. The recently developed microRNA biomarker (let-7 and ATP11B) which is linked to

platinum drug resistance is one such example. Hence primary focus must be the development of prominent biomarkers in ovarian cancer for apoptosis with increased specificity and sensitivity.

Acknowledgements

Authors are thankful to the high computational facility at Department of Computer Science Jamia Millia Islamia. AB is thankful to ICMR (Indian Council of Medical Research; PROJECT ID: 2019-4178) for the funding the research.

Fundings

This work was supported by Indian Council of Medical Research; PROJECT ID: 2019-4178

References

1. Zhang X. Omics technologies in cancer biomarker discovery. (1stedn). CRC Press. London. UK. 2011;pp1-150.

2. Lõhmussaar K, Kopper O, Korving J, et al. Assessing the origin of high-grade serous ovarian cancer using CRISPR-modification of mouse organoids. Nat Commun. 2020;11:1-14.

3. Pau G, Fuchs F, Sklyar O, et al. EBImage-an R package for image processing with applications to cellular phenotypes. J Bioinform. 2010;26:979-81.

4. Desbois M, Udyavar AR, Ryner L, et al. Integrated digital pathology and transcriptome analysis identifies molecular mediators of T-cell exclusion in ovarian cancer. Nat commun. 2020;11:1-14.

5. Aparna C, Santanu C. Role of bioinformatics in cancer. 2010;47:46-8.

6. Zhu J, Chen Z, Yong L. Systematic profiling of alternative splicing signature reveals prognostic predictor for ovarian cancer. Gynecol oncol. 2018;148:368-74.

7. Venables JP, Klinck R, Koh CS, et al. Cancer-associated regulation of alternative splicing. Nat Struct Mol Bio. 2009;16:670-6.

8. Liu J, Lv D, Wang X, et al. Systematic profiling of alternative splicing events in ovarian cancer. Front Oncol. 2021;11:1-11.

9. Lam HY, Clark MJ, Chen R, et al. Performance comparison of whole-genome sequencing platforms. Nat biotechnol. 2012;30:78-82.

10. Asmann YW, Middha S, Hossain A, et al. TREAT: a bioinformatics tool for variant annotations and visualizations in targeted and exome sequencing data. Bioinformatics. 2012;28:277-78.

11. Fischer M, Snajder R, Pabinger S, et al. SIMPLEX: cloud-enabled pipeline for the comprehensive analysis of exome sequencing data. PloS one. 2012;7:1-8.

12. Palaia I, Tomao F, Sassu CM, et al. Immunotherapy for ovarian cancer: recent advances and combination therapeutic approaches. Onco Targets Ther. 2020;13:6109-29.

13. Beg A, Khan FI, Lobb KA, et al. High throughput screening, docking, and molecular dynamics studies to identify potential inhibitors of human calcium/calmodulin-dependent protein kinase IV. J Biomol Struct Dyn. 2019;37:2179-92.

14. Mohammad T, Khan FI, Lobb KA, et al. Identification and evaluation of bioactive natural products as potential inhibitors of human microtubule affinity-regulating kinase 4 (MARK4). J Biomol Struct Dyn. 2019;37:1813-29.

15. Xu S, Grande F, Garofalo A, et al. Discovery of a novel orally active small-molecule gp130 inhibitor for the treatment of ovarian cancer. Mol Cancer Ther. 2013;12:937-49.

16. Astorgues-Xerri L, Riveiro ME, Tijeras-Raballand A, et al. OTX008, a selective small-molecule inhibitor of galectin-1, downregulates cancer cell proliferation, invasion and tumour angiogenesis. Eur J Cancer. 2014;50:2463-77.

17. Lin ZP, Zouabi NNAl, Xu L, et al. In silico screening identifies a novel small molecule inhibitor that counteracts PARP inhibitor resistance in ovarian cancer. Sci Rep. 2021;11:1-21.

18. Kashani B, Zandi Z, Bashash D, et al. Small molecule inhibitor of TLR4 inhibits ovarian cancer cell proliferation: new insight into the anticancer effect of TAK-242 (Resatorvid). Cancer Chemother Pharmacol. 2020;85:47-59.

19. Eichborn JV, Woelke AL, Castiglione F, et al. VaccImm: simulating peptide vaccination in cancer therapy. BMC bioinform. 2013;14:1-9.

20. Yang C, Xia B-R, Zhang Z-C, et al. Immunotherapy for ovarian cancer: adjuvant, combination, and neoadjuvant. Front Immunol. 2020;11:1-18.

21. Berry DA, Iversen Jr ES, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol. 2002;20:2701-12.

22. Bonn D. Prostate-cancer screening targets men with BRCA mutations. Lancet Oncol. 2002;3:714.

23. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817-26.

24. Dann RB, DeLoia JA, Timms KM, et al. BRCA1/2 mutations and expression: response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. Gynecol Oncol. 2012;125:677-82.

25. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366:1382-92.

26. Petricoin EF, Liotta LA. SELDI-TOF-based serum proteomic pattern diagnostics for early detection of cancer. Curr Opin Biotechnol. 2004;15:24-30.

27. Srinivas PR, Verma M, Zhao Y, et al. Proteomics for cancer biomarker discovery. Clin. Chem. 2002;48:1160-9.

28. Yu JK, Zheng S, Tang Y, et al. An integrated approach utilizing proteomics and bioinformatics to detect ovarian cancer. J Zhejiang Univ Sci B. 2005;6:227-31.

29. Zhang Z, Bast Jr RC, Yu Y, et al. Three biomarkers identified from serum proteomic analysis for the detection of early-stage ovarian cancer. Cancer Res. 2004;64:5882-90.

30. Kumar SU, Kumar T, Shiva R, et al. Integrative bioinformatics approaches to map potential novel genes and pathways involved in ovarian cancer. Front Bioeng biotechnol. 2019;7:1-15.

31. Xue J, Yang G, Ding H, et al. Role of NSC319726 in ovarian cancer based on the bioinformatics analyses. OncoTargets ther. 2015;8:1-9.

32. Li Y, Wang Q, Ning N, et al. Bioinformatic analysis reveals MIR502 as a potential tumour suppressor in ovarian cancer. J Ovarian Res. 2020;13:1-16.

33. Beg A, Parveen R. Role of bioinformatics in cancer research and drug development. In: Raza K, Dey N (eds). Translational Bioinformatics in Healthcare and Medicine. (1stedn). Academic Press Inc. 2021;pp.1-254.

34. Ko S, Choi J, Ahn J. GVES: machine learning model for identification of prognostic genes with a small dataset. Sci Rep. 2021;11:1-8.

35. Schmauch B, Romagnoni A, Pronier E, et al. A deep learning model to predict RNA-Seq expression of tumours from whole slide images. Nat Commun. 2020;11:1-16.

36. Chang JT, Nevins JR. GATHER: a systems approach to interpreting genomic signatures. Bioinformatics. 2006;22:2926-33.

37. Md Hossain A, Sk Islam MS, Quinn JMW, et al. Machine learning and bioinformatics models to identify gene expression patterns of ovarian cancer associated with disease progression and mortality. J Biomed Inform. 2019;100:1-11.

38. Yang X, Zhu S, Li L, et al. Identification of differentially expressed genes and signaling pathways in ovarian cancer by integrated bioinformatics analysis. Onco Targets Ther. 2018;11:1457-74.

39. Sheikhvatan M, Chaichian S, Moazzami B. A Systematic review and bioinformatics study on genes and micro-RNAs involving the transformation of endometriosis into ovarian cancer. MicroRNA. 2020;9:101-11.

40. Behl T, Kaur I, Sehgal A, et al. Bioinformatics accelerates the major tetrad: a real boost for the pharmaceutical industry. Int J Mol Sci. 2021;22:1-28.