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RESEARCH ARTICLE

Biomarkers, Methods for Detection and Treatment of Breast Cancer.

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Abstract

Irritation expects a separating part in different sorts of advancement and is known prohibited in their presentation and progress. Like this, it is in a matter of seconds saw as a vital danger part of a few sorts of diseases, for the case, "bladders, prostrate and Breast"improvements. The disclosure of a novel technique for affirmation Breast hurt malady in the investigation office Moreover in easing mixes can have the colossal repercussions for the treatment of advancement and, likewise, preventive and mindful treatment modalities. Breast improvement is the most every now and again analyzed risk and the second driving reason behind tumor-related passings. Updated insight of Breast tumorigenesis may improve the movement of all the more serious prescriptions. The clinical and over the top qualities of this Breast improvement subtype is not yet totally gotten on. This study was given a development of essential, preclinical and clinical studies. As a sure biomarker of reaction to a Breast risk, we recognized this acumen reaction of tumor cells in the Breast.

Introduction:-

More studies are facilitated to understand the impact of Breast advancement, particularly in right on time affirmation. From this time forward in the present study, we have attempted, generally, to investigate the biomarkers as parameters on Breast advancement. Likewise, was to use to measure the most modest clear structures that could be perceived by in a matter of seconds open biomarker tests. The second and a key target was to see biomarker-related rules that effect early disease affirmation and to evaluate through an examination office test fundamentals must be balanced [amplified or decreased] to enhance it. The creators picked as the objective for more affirmation and revelation of the novel system for recognizing evidence Breast tumor burden in the investigation. The workplace can comparably pass on in human tissues, and are valuable in biomarkers for Breast hurt. Our goal was asymptomatic Breast advancement biomarker and as a manual for the sub-depiction of unmistakable Breast risk.

Biomarkers:-

1- E-cadherin and β-catenin:-

Cadherins and catenins are hormonally regulated and carry out physiological roles during mammary development but have pathological effects when deregulated [**1]**. Catenins are lost or mislocalized in tumors lacking cadherins. E-cadherin is invasion-related protein. The first step in the metastatic cascade is loosening of tumor cells. E-cadherin acts asintercellular glueand mediateshemophilic, calcium dependent cell-cell adhesion. Its cytoplasmic portion binds to β-catenin, which connects the adhesion complex to the actin cytoskeleton. The E-cadherin/catenin-mediated cell adhesion system is known to act as an "invasion suppressor system". A reduced or absent expression or abnormal location of E-cadherin/catenin complex has observed in several carcinomas including breast cancer **[2].**

E-cadherin-mediated cell-cell adhesion prevents cells in a primary tumor from breaking away and invading near or distant sites. It has well documented that loss of E-cadherin in mammary epithelial cells can promote breast cancer

progression and metastasis. Evaluation of E- cadherin helps in predicting the prognosis of invasive ductal breast carcinomas **[3].**
Immunohistochemistry investigated protein expressions of these molecular markers. Theimmunostaining of E-cadherin and β-catenin in normal breast epithelial cells showed uniform strong linear membrane staining. Breast carcinomas revealed a heterogeneous staining for E-cadherin and β-catenin. Staining was confined notonly to themembrane but also present diffusely in the cytoplasm **[2].**

Matrix metalloproteinase 1:-
An important step in the metastatic cascade is local degradation of the basement membrane [BM] andextracellular matrix. Tumor cells either directly secret proteolytic enzymes or induce the stromal cells such as fibroblasts and vascular endothelial cells to secret proteolytic enzyme that handle such BM degradation **[2].**
The matrix metalloproteinases [MMPs] are a large family of proteolytic enzymes. MMPs are usedby invasivecancer cells to hydrolyze the structural proteins that comprise the extracellular matrix such as collagen, elastin, laminin, fibronectin and fibrinogen **[4].** In particular, matrix metalloproteinase 1 [MMP-1][interstitial collagenase], which can degrade types 1, 2, and three collagens, is closely correlated with the invasive and metastatic potentials of various cancers. High levels of MMP-1 mRNAare correlated with poor prognosis in breast cancer patients **[5].** In normal adult tissues, the mRNA levels of MMP-1 are usually low. So that elevated MMP-1 expression in atypical ductal hyperplastic tissues is expected to serve as a predictive marker for the future development of invasive breast cancer and metastasis. In breast cancer, a high MMP-1 protein level has been demonstrated to be associated with lymph vascular invasion. An increased MMP-1 expression level has associated with the malignancy or invasiveness of severalcancers, suggesting that measures blocking MMP-1 may be beneficial in the treatment of breast cancer **[6].**

3-peroxiredoxins:-
The peroxiredoxins [Prx] are a family of 25 kDa peroxidases that can reduce H2O2 using an electron from thioredoxin or other substances. The mammalian Prx family divided into six groups [Prx I-VI] on the basis of the homology of amino acid sequences. They located in the cytosol and play a role in the cell signaling system. Prx overexpressed in breast cancer tissues to a great extent suggesting that Prx has a proliferative effect and may be related to cancer development or progression **[7].** The PRDX6 gene located on chromosome 1q2, it is an important antioxidant enzyme and has a major role in lung phospholipid metabolism. PRDX6 stably overexpressed in cells protected against oxidative stress, whereas antisense treatment resulted in oxidant stress and apoptosis **[8].**

PRDX6 is one of the proteins with different levels of expression. Overexpression of PRDX6 leads to a more invasive phenotype and metastatic potential inhuman breastcancer [**9].** A crucial step in invasion and metastasis is the destruction of biological barriers, such as the basement membrane, which requires activation of proteolytic enzymes. Many studies have shown that enhanced production of members of the plasminogen activator pathway and MMP family contributed to tumor invasion, metastasis, and angiogenesis. The uPAR could regulate cell-surface-associated proteolysis by uPA, and it also involved in the regulation of cell adhesion and migration independent of the enzymatic activity of its ligand **[10].** Upregulated expression of the uPAR, but not uPA, was associated with increased tumor cell invasion and metastasis in breast cancer by PRDX6. By contrast, downregulated expression of the uPAR associated with decreased tumor cell invasion and metastasis **[11].**

MMP activity is tightly regulated by specific physiological inhibitors, TIMPs [tissue inhibitor of MMP][Kim et al., 2006]. The TIMP family comprises at least four distinct members: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Ets-1[E26 transformation-specific-1] is a member of the Ets family of transcription factors. It has reported that Ets-1 overexpressed in a variety of human malignancies, including breast cancers **[12].** Because of its roles in the transcriptional regulation of MMPs, Ets-1 is a candidate mediator of cancer invasion and metastasis. The enhancement of invasive phenotype of breast cancer cells by PRDX6 accompanied by upregulation of MMP-9 and Ets-1 expression and downregulation of TIMP-2 expression. However, no significant differences in expression of other members of the MMP and TIMP families were found among PRDX6-transfected, knockdown, and parental cells. PRDX6 might stimulate the upregulation of MMP-9 through activation of Ets-1 and deactivation of TIMP-2 **[11].**

4- Cathepsin D:-
Cathepsin D, an estrogen-inducible protein, is a lysosomal protease. Is considered to be involved in the breakdown of the extracellular matrix during the process of tumor metastasis **[13].** Cathepsin D gene expression induced by growth factors, such as epidermal growth factor. Insulin-Like Growth Factor 1 and basic fibroblast

growth factor **[14].** Cathepsin D investigated in breast cancer by immunohistochemistry. Immunostaining for Cathepsin D appeared as fine to coarse granular cytoplasmic staining in tumor cells and stromal cells. Cathepsin D was positive in 40.9% cases of cancer cells and 67.4% cases of stromal cells. Positive staining of Cathepsin D in cancer cells strongly associated with age, often in younger age group [≤50 years] than in older age group [>50 years][59.0% vs. 27.8%]. Positive stromal staining of Cathepsin D in stage III tumors was much higher than that in early stage tumors [stage I and stageII]. Cathepsin D shown in stromal cells but not the tumor cells correlates significantly with poor prognosis **[2]**. Cathepsin D might be a useful marker to discriminate between ductal and lobular subtypes of breast cancer. Ductal carcinomas showed a significantly higher immunohistochemically reaction compared to lobular carcinomas **[13].**

5- Alpha B-crystalline:-

The small heat shock protein alpha -basic–crystalline [alpha B- crystalline] isa novel oncoprotein. Alpha B-crystalline is commonly expressed in basal-like breast carcinomas and predicts shorter survival **[15].** Basal-like tumors are a newly recognized estrogen receptor negative and HER2 negativebreast cancersubtype that expresses basal epithelial genes and associated with poor survival. **[16].**

Alpha B-crystalline expressed by immunohistochemistry, was restricted to the myoepithelial cell compartment of ductal and lobular units. Most basal-like and metaplastic carcinomas demonstrated cytoplasmic expression of alpha B-crystallin [81% and 86%, respectively]. Conversely, no staining for alpha B-crystallin was observed in nonbasal-like [ER positive or HER2 positive] breast carcinomas. Alpha B-crystallin is a sensitive [81%] and specific [100%] marker for basal- like breast carcinomas. The high rates of expression of alpha B-crystallin in metaplastic breast carcinomas [86%] suggest that these tumors may represent a distinctive histological subset of basal-like breast tumors with a similar underlying molecular etiology **[17].**

Alpha B-crystallin expression predicts poor survival in breast cancer patients independently of traditional prognostic factors, including tumor grade, tumor size, lymph node status, and ER or HER2 status [15].

6- Metallothionein:-

Metallothionein [MT] genes are transcriptionally activated by the essential metal zinc as well as by environmental stresses, including toxic metal overload and redox fluctuations. In addition to playing a key role in zinc homeostasis, MT proteins can protect against metal- and oxidant- induced cellular damage. May participate in other fundamental physiologic and pathologic processes such as cell survival, proliferation, and neoplasia [18]. MT a family of low molecular weight metal binding proteins encoded by at least ten functional MT genes. Subdivided into four groups, MT-1, MT-2, MT-3, and MT-4 that associated with cell proliferation in breast cancer. MTs are known to participate in cell proliferation, a process that is believed to be important in carcinogenesis **[19].** Expression of the MT protein has detected by immunohistochemistry. MT positivity associated with poor prognosis, shorter overall survival and a more aggressivephenotype. Higher MT expression in breast cancers is predictive of worse patient outcomes and tamoxifen resistance in invasive ductal breast cancer **[20].**

7-The extracellular matrix protein [ITIH5]:-

Inter-alpha-trypsin inhibitors [ITIs] are protease inhibitors stabilizing the extracellular matrix. ITIs consist of one light [bikunin] and two heavy chains [ITIHs]. ITIH5, a novel member of the ITIH gene family. It showed that its messenger RNA is lost in a high proportion of breast tumours. Loss of ITIH5 expression is associated with unfavorable outcome in breast cancer patients and thus ITIH5 could be used as a prognostic marker **[21].** An ITIH5 specific polyclonal antibody was generated, validated with western blot and used for immunohistochemically analysis on a tissue microarray. ITIH5 was strongly expressed in epithelial cells of normal breast while it was lost or strongly reduced in 42% of invasive breast cancers. ITIH5 expression in invasive carcinomas was associated with positive expression of estrogen receptor and histological grade **[22].**Correlation of ITIH5 expression with clinical outcome revealed that patients with primary tumours retaining abundant ITIH5 expression had longer recurrence-free survival and overall survival, compared to those with reduced expression. ITIH5 is a tumours suppressor gene and could be involved in tumours progression, invasion and metastasis. Its absence is associated with increased proliferation rates and a prognostic value indicating poor clinical outcome **[21].**

8-Colony Stimulating Factor-1:-

Colony stimulating factor-1 [CSF1] and its receptor [CSF1-R] are important in mammary gland development and have been implicated in breast carcinogenesis. breast cancer risk varied by menopausal status, CSF1 levels in the highest [versus lowest] were associated with an 85% reduced risk of premenopausal breast cancer, in contrast, CSF1 levels in the highest conferred a 33% increased risk of postmenopausal breast cancer. Thus, the association of

circulating CSF1 levels and breast cancer varies by menopausal status. CSF-1 is produced by a variety of cells and stimulates the proliferation, differentiation, and survival of cells of the mononuclear phagocytic lineage. CSF-1 plays a role in mammary gland physiology because it is synthesized by the mammary ductal epithelium and macrophages recruited by CSF-1 promote both mammary ductal invasions during puberty and lobuloalveolar differentiation during pregnancy. A paracrine CSF-1 loop, therefore, exists in the normal mammary gland. Enhanced recruitment of macrophages to mammary tumors on one hand and the poor prognosis associated with elevated tumor associated macrophages on the other suggested a role for CSF-1 and CSF-1-regulated macrophages in breast cancer **[23].** An increase in tumor-associated macrophage density is correlated with poor prognosis. Based on these biological properties of CSF-1, using antisense constructs to block CSF-1 transcription in solid tumors, including mammary cancer and showed that this treatment resulted in significant suppression of tumor growth. By using of neutralizing anti- CSF-1 antibodies in combination with chemotherapy, tumor development was suppressed by 56% and long-term survival was significantly prolonged **[24].**

9-Thymidine phosphorylase:-

Thymidine phosphorylase [TP] stimulatedchemotaxis of endothelial cells and involved in the angiogenesis of human solid tumors. Nuclear and cytoplasmic TP expression observed in tumor cells by immunohistochemically expression of thymidine phosphorylase protein. Immunoreactivity was also present in the stroma, endothelium, and tumours-associated macrophages. TP expression does not seem to affect directly the neovasculature of breast carcinoma, although it seems to implicate in the remodeling of breast cancer tissue. Through the interaction with other extracellular matrix components [tenascin, fibronectin, collagentype IV and laminin] orproteolytic enzymes. Tumor cell TP expression could considered as a prognostic indicator of breast cancer patients **[25].** TP localization investigated in breast cancer tissue by immunohistochemistry and its ultrastructural localization by immunoelectron microscopy **[26].** TP was diffusely positive in the cytoplasm of cancer cells and specifically positive in mitochondria of neutrophils and specific cytoplasmic granules of macrophages in cancer tissue by immunoelectron microscopy. These findings suggest that TP is produced by macrophages and is present in mitochondria of neutrophils and cytoplasmic granules of cancer cells.TP is prognostic and predictive in early stage breast cancer patients **[27].**

10- CDK1 and CDK2:-

In eukaryotic cells, cyclin-dependent kinase [CDK] complexes regulate the temporal progression of cells through the cell cycle. Deregulation of the cell cycle is one of the hallmarks of tumor formation and progression **[28].** Cyclin-dependent kinases [CDKs] expressed almost constantly, but their activities change according to cell cycle phase. The specific activity [SA, activity/expression] of CDKs evaluate their role in cell proliferation. The ratio of CDK2 SA to CDK1 SA has associated with rapid tumor growth in human breast cancer. Tumors grouped as low, intermediate and high CDK2/1 ratio. The high CDK2/1 ratio associated with worse prognosis than the low CDK2/1 ratio **[29].** Tumors with high CDK1 SA and high CDK2 SA showed significantly poorer 5- year relapse-free survival than those with low CDK1 SA and low CDK2 SA. Moreover, combined analysis of CDK1 SA and CDK2 SA enabled the classification of breast tumors into high- risk and low-risk groups. Where tumors in the high-hazard aggregate firmly connected with unfavorable forecast [5-year backslide free survival 69.4% for the high-hazard bunch and 91.5% in the safe gathering].The risk determined by combined analysis of CDK1 SA and CDK2 SA is a significant prognostic indicator for relapse, especially in node-negative patients. For patients with node- negative disease, especially those with hormone receptor-positive tumors gave adjuvant hormone therapy alone. The CDK2/1 ratio might be useful as a routine laboratory test to predict the outcome **[30].**

11-Cyclin E:-

Cyclin E closely linked to proliferation, elevated levels of cyclin E protein have fairly consistently associated with a poor prognosis in breast cancer **[31].** The cyclin E gene amplified in some breast cancer cell lines. The most significant cyclin E alteration is the post-translational cleavage of full-length cyclin E by a protease into low molecular weight [LMW] forms that areHyperactive compared to the full-length protein. Some Breast tumor cell lines and human Breast malignancies express up to 5 LMW isoforms of cyclin E [running in size from 34 to 49 kDa], notwithstanding overexpressing the 50 kDa full-length cyclin E protein.

These LMW forms are unique to tumor cells and correlate with increasing stage and grade of breast cancer **[32].** These LMW forms of cyclin E1 show higher CDK2 kinase activity and the low molecular weight cyclin E1/CDK2 complexes are more resistant to inhibitors and antiestrogens. Levels of total cyclin E1 and low molecular weight cyclin E1 in tumor tissue measured by Western blot assay correlated strongly with survival in patients with breast cancer **[33].** Cyclin E was a better prognostic indicator than nodal status and even for stage I patients who all had

negative lymph nodes, cyclin E was the best indicator of outcome. Cyclin E is a predictive factor in breast cancer management and used as a target for therapy **[34].**

12-circulating cell-free DNA:-

The integrity of circulating cell-free DNA [cf-DNA] in serum or plasma appears to be of diagnostic and prognostic value in cancer. The integrity of serum DNA was higher in patients with increasing DNA levels and vice versa **[35].** Tumor-related cell-free DNA circulating in the blood is a biomarker for malignant tumor detection or prognosis. Absolute levels of circulating DNA detected in serum/plasma related to presence and prognosis of breast cancer. Methylation of tumor suppressor genes detected in circulating DNA has demonstrated prognostic potential. It was that integrity of circulating DNA, measured as the ratio of longer to shorter DNA fragments, is higher in patients with gynecologic and breast cancers than in normal individuals **[36].**

Apoptotic cells release DNA fragments that are usually 185 to 200 base pair [bp] in length. This uniformly truncated DNA is produced by a program enzymatic cleavage process during apoptosis. In healthy individuals, the main source of free circulating DNA is apoptotic cells. In contrast, DNA released from malignant cells varies in size because pathologic cell death in the malignant tumors results not only from apoptosis, but also necrosis, autophagy, or mitotic catastrophe **[37].** Therefore, elevated levels of long DNA fragments may be a good marker for detection of malignant tumor DNA in blood. The serum DNA integrity measured by quantitative real-time PCR [qPCR]. Serum was considered a better source of circulating DNA than plasma because serum contains the significantly higher amount of DNA with a low level of contaminating extraneous DNA released from leukocytes. Serum DNA integrity was useful for preoperative prediction of regional LN metastasis in breast cancer and directly correlated with breast cancer staging. Integrity of serum circulating DNA is a promising molecular biomarker for detecting breast cancer tumor progression and regional lymph node metastases **[38]**

13- Cytosine-methylation:-

Cytosine methylation changes are stable and thought to be among the earliest events in tumorigenesis. DNA carrying tumor-specifying methylation patterns escape the tumors and may be found circulating in the sera from cancer patients. Thus providing the basis for the development of noninvasive clinical tests for early cancer detection **[39].** Cytosine methylation is a centrally important DNA modification for the maintenance of large genomes. The central importance of proper DNA methylation maintenance highlighted in diseases such as cancer, where the normal patterns lost. DNA that normally methylated becomes unmethylated while DNA that is supposed to be methylation free obtains the modification **[40].**

This apparent redistribution of normal methylation patterning is regionally complex and is thought to be among the earliest molecular alterations during tumorigenesis. Therefore, abnormal methylation marks may be useful as biomarkers for the early detection and diagnosis of different types ofcancer [**41].** The serum is a very attractive medium for the development of cancer detection assays as obtained through a simple, relatively noninvasive procedure. The circulating DNA could come from intact tumor-derived cells found in blood and from the tumor itself through releases of DNA into the bloodstream via necrotic or apoptotic pathways **[42].** Genetic mutations in BRCA1 and BRCA2, CHEK2, ATM, and TP53, result in increased risk of breast cancer. However, these are estimated to account for only 5% to 10% of breast cancer cases. A recent large-scale sequencing analysis of over 13,000 genes in a small collection of breast tumors identified 122 genes with somatic mutation frequencies higher than the background frequency. However, each tumor harbored only a few mutations, and no single mutation or combination of mutations predominated across the tumor samples **[43].** In addition to genetic alterations, epigenetic abnormalities such as changes in genomic DNA cytosine methylation patterns are associated with all cancer types. The spectrum of alterations includes both gain and loss of DNA methylationinvolving multi-copy elements aswell as single-copy genes. Many of the changes affect gene expression and genome stability through inappropriate regulation of local chromatin structure suggest that epigenetic changes involved in the earliest phases of tumorigenesis. They may predispose stem/progenitor cells to subsequent genetic and epigenetic changes involved in tumor promotion **[40].** DNA methylation changes in tumorigenesis and the inherent stability of the molecular abnormality. These events may provide ideal biomarkers for molecular diagnostics and early detection of cancer. Several genes have aberrantly methylated in breast cancer, for example, Ras association domain family member 1A [RASSF1A]. Most commoloisne of the epigenetically silenced tumor suppressor genes in human cancer that controls cell cycle and apoptosis. RASSF1A methylation in breast cancer, the average frequency at which hyper methylation detected in brass t tumors is 56% **[44].** The differential cytosine methylation events were independent of patient age, tumor stage, estrogen receptor status or family history of breast cancer. The identification of a single

differentially methylated locus, associated with the GHSR [Growth hormone secretagogue receptor] gene. Capable of distinguishing infiltrating ductal breast carcinoma from normal and benign breast tissues with a sensitivity and specificity of 90% and 96%. The frequency of these molecular abnormalities in breast tumors substantially exceeds the frequency of any other single genetic, or epigenetic change reported to date. The discovery of over 50 novel DNA methylation based biomarkers of breast cancer may provide new routes for development of DNA methylation based diagnostics and prognostics. As reveal epigenetically regulated mechanism involved in breast tumorigenesis **[41].**

14-Ki-67:-

Ki-67 is a no histone protein expressed in cells. Uncontrolled proliferation is the key element of malignant transformation. MIB-1, an epitope of the Ki-67 protein. The MIB-1 [Ki-67] nuclear antigen expressed in the late phase G1 [gap 1], phases S [synthesis] G2 [gap 2], and M [mitosis] phases of continuously cycling cells. But is absent in G0 [quiescent phase] cells and the early G1 phases **[42].** Therefore, immunostaining with monoclonal antibody MIB-1 serves as a measure of cell proliferation. This index is the most practical method of monitoring cell proliferation. The Ki-67 correlates with the S-phase of the cell cycle and the mitotic index. Tumorswith high cell proliferation should respond well to chemotherapy. Breast cancers with high Ki-67 expression responded well to primary chemotherapy. The absence of hormone receptors and Ki-67 $\geq$ 20% in post neoadjuvant chemotherapy specimens was predictive of complete response **[43]**. Ki-67 correlated positively with tumor grade. High expression of Ki-67 may determine poor prognosis, especially in node-negative patients. Ki-67 gene expression identified by a real-time RT-PCR assay, which is considered one of the most reliable methods for detecting mRNA. Recently, real-time RT-PCR was used for determining prognosis in breast cancer **[44].**

15- Topoisomerase II:-

Topoisomerase II [Topo II] located on chromosome 17 [17q21- q22] close to HER2. The enzyme is a molecular target for anthracyclines. Shows alterations [Amplificationor deletion] in HER-2 amplified tumors. Topo II is an enzyme involved in cellular transcription, replication and repair processes, by twisting and supercoiling specific regions of DNA. Topo II is a target of anthracyclines and has proposed as a chemo sensitivity marker of anthracycline-containing therapies **[45].** A significant proportion of breast cancers with HER2 amplification show simultaneous amplification or deletion of topo II. Amplification of topo II may lead to the overexpression of the topo II protein and hypersensitivity to topoII inhibitors. Response to chemotherapy apparently increased in HER2-amplified breast cancer, and the therapeutic efficacy further increased by topoII-so amplification, finding a chromogenic in situ hybridization [CISH] method. HER2 and topo II amplification significantly associated with the response to chemotherapy. Chemotherapy is highly effective in breast cancers that have amplification of HER2 and topoII. In contrast, the clinical response was significantly decreased in breast cancers without HER2 and topoII amplification **[46].**

Methods for detection:-

Classical clinical andhistological parametershave beenused to predict survival, development of metastatic disease and direct therapy of breast cancer. For decades, path-biologic parameters such as histological grade, tumor size, lymph node involvement, estrogen receptor α, and HER2 receptor status. All of which influence prognosis, have been used to predict the benefit of systemic therapies, but they do not fully capture the varied clinical course of breast cancer [47]. Although many conventional techniques are helpful tools to prognosticate a particular tumor's behavior, there remains substantial variability in disease outcomes within each predictive category. Furthermore, these variables are not helpful in selecting the optimal chemotherapy regimen. The different clinical course of patients with histologically similar tumors is believed to be due to their molecular differences. Therefore, the molecular analysis of breast cancers should yield more accurate diagnostic and prognostic results that will likely result in more precise treatment options for patients [**47].**

In the treatment of cancer, there is a shift from the traditional clinical practices to novel approaches. Traditionally, cancer patients were treated with drugs of low toxicity or of high tolerance regardless of their efficacy in a given patient if the benefits of that drug proven in both experimental and clinical conditions. However, recent advances in basic and clinical research have provided opportunities to develop 'personalized' treatment strategies. These novel approaches are intended to identify individualized patient benefits of therapies, minimize the risk of toxicity and reduce the cost of treatment **[48].**

1-Enzyme-Linked Immunosorbent Assay [ELISA]:-
ELISA is a biochemical technique used mainly in immunology to detect the presence of an antibody or an antigen in a sample. In ELISA, an unknown amount of antigen is affixed to a surface, and then a specific antibody is washed over the surface so that it can bind to the antigen. This antibody linked to an enzyme, and in the final step a substance is added that the enzyme can convert to some detectable signal. Thus in the case of fluorescence ELISA, when a light of the appropriate wavelength shone upon the sample. Any antigen/antibody complexes willfluoresce sothat the amount of antigen in the sample can infer from the magnitude of the fluorescence. Example HER2 oncoproteinlevels [Shed antigen in the serum], p53 protein overexpression measured by ELISA **[49].**Immunohistochemically[IHC] staining techniques developed more than 25 years ago. Currently the cornerstone for classifying breast cancers into ER positive and ER negative categories. Measuring protein overexpression of HER-2, Ki67, p53, Cathepsin D. IHC positivity for HER-2and p53 is associated with a worse prognosis **[50].**

2-In situ hybridization:-
The method of molecular genetic analysis has incorporated in diagnostic breast pathology laboratories. ISH is a molecular technique that has been available since 1969. Unlike other techniques for molecular genetic analysis. ISH is unique in that it based on a visual assessment of probe copy numbers using microscopic visualization and can be performed directly on metaphase and interphase nuclei **[51].**

3-Fluorescent in situ hybridization [FISH] and chromogenic in situ hybridization [CISH]:-
FISH can used for the identification of gene gains, losses, translocations, and amplification whereas CISH best suited for the identification of gene amplification **[52].** Both FISH and CISH rely on the property that denatured DNA probes can hybridize specifically to denatured, complementary target DNA. As the name suggests, the main difference between FISH and CISH is how the probe signals visualized. FISH employs fluorochromes for signal identification, whereas CISH uses chromogens. Detection of HER2 gene amplification, Topoisomerase II amplification by FISH and CISH **[53].**

4-Polymerase chain reaction [PCR]:-
Various techniques have been used; including differential , competitive, real- time PCR and Quantitative reverse transcriptase-polymerase chain reaction [RT-PCR]. RT-PCR is a valuable assay that requires small amounts of tissue for the analysis of RNA expression. Example quantitative real-time PCR used to detect mRNA expression of mammaglobin, uPA and its inhibitor PAI-1 **[54].**

5-High-throughput technologies:-
Laboratory-based techniques for detecting the molecular and genetic changes are expensive and time-consuming. In populations, automation, and cost- effectiveness has to be built technologies to make them viable screening tools for use. Also, minute amounts of a biomarker should be detectable with high precision. Recent advances in genomics and proteomics hold great potential for diagnostic, prognostic, and therapeutic applications **[55].**

6-Proteomic analysis for breast cancer:-
Different clinical states, including cancer, might be represented by distinct protein patterns, or signatures. These signatures might consist of completely different proteins, of various mixtures of truncated peptide fragments. Modifications of proteins or peptides, such as glycosylation, cysteinylsation, lipidation, and glutathionylation, each of which might be cancer specific. Therefore, one might be able to exploit these differences, either in tissue, in the circulation, or in secreted fluids, for diagnostic purposes. For proteomic pattern analysis, computer-based algorithms have been developed to distinguish breast cancer from benign disease, or to identify individuals at high risk of recurrence based on the pattern of peptide peaks. An alternative method uses proteomic methods to identify a limited number of proteins that can measured by immunohistochemical or serum- based immunoassays. Markers can then be validated individually or in combination as a profile or signature **[31].**

There are several different approaches to analyzing multiple proteins or peptide fragments simultaneously, and each has its positive and negative features **[56].** However, the most widelyStudied methods involve identification of proteomic profiles as peaks on mass spectrometric analysis of precise charge-to-mass ratios. In some cases, proteins have been designated by their apparent molecular weight and isoelectric point within two-dimensional [2D] gel analysis. Specific peptides can be identified further based on their amino acid sequence identity or homology to known proteins or their fragments. Peptides have been identified in serum from breast cancer patients **[57];** drug-

resistant breast cancer cell lines; cancer cell line membranes; nipple aspirate fluid [NAF]; and normal, benign, premalignant, and malignant tumor tissue **[58].** For analysis of breast cancers, some studies have used whole tumor specimens that include both epithelial cells and stroma, whereas others have used micro dissected epithelial cells. If isolation of epithelial cells is not required, fine-needle aspirate has obtained adequate material. Before mass spectroscopic analysis, preliminary separation of proteins can be performed with 2D gel analysis **[59].** Binding of proteins to surfaces or matrices using surface-enhanced laser desorption and ionization [SELDI]**[57]** and matrix-associated laser desorption and ionization [MALDI], **[59]** respectively. After desorption and ionization, the pattern of charged peptides generally has been analyzed by time-of-flight [TOF] mass spectroscopy. Other methodologies to examine multiple proteins at once have used multiplex ELISAs that can detect several different proteins simultaneously. Similar assays using phage displays or aptamers to detect multiple peptides **[31].**

7-Genomics:-
Defined as the measurement of gene expression from available sequence information. Technological advances in biomolecular assays in a miniature format on glass, silicon, or even beads of fiber-optic bundles **[60]** have accelerated the development of genomics. Complementary DNA [cDNA] and oligonucleotide microarrays on chips and serial analysis of gene expression [SAGE] are recently developed techniques in genomics **[55].**

8-**Microarray analysis:-**
Microarray analysis is a method that compares gene expressions between normal and cancerous cells, and is stimulating the discovery of new targets in the treatment of breast cancer **[47].**

9-Tissue microarrays:-
The microarray studies have relied on fresh-frozen tissue samples. This material is difficult to collect, cumbersome to process, and expensive to store. In the past few years, there has been great progress in developing technologies to utilize formalin-fixed paraffin embedded tissue samples for gene expression and proteomic analysis. Formalin-fixed paraffin-embedded tissue samples routinely used for IHC analysis and are currently being used in the Oncotype DX assay **[61].** Tissue microarray analysis has also been used to classify breast cancers into subgroups as to provide prognostic significance **[62].** BRCA1 and BRCA2 tumors have also been subjected to tissue microarray analysis. BRCA1 is characterized as having a basal phenotype; ER-negative and HER2, Negative, with up-regulation of cyclin A and caspase 3, and down-regulation of BCL2, cyclin D1 and D3. In contrast, most BRCA2 tumors are ER-positive, PR-positive, with up-regulation of BCL2, cyclin D1 and D3 **[63].**

Treatment:-
The three major treatments of breast cancer are surgery, radiation, and drug therapy. The treatment for breast cancer is surgery when the tumor is localized, with possible adjuvant hormonal therapy [with tamoxifen or an aromatase inhibitor], chemotherapy, and/or radiotherapy **[64].**

1-Surgery to the breast:-
Depending on the staging and type of the tumor, just a lumpectomy [removal of the lump only], or mastectomy [surgical removal of the entire breast] plus radiotherapy **[65].**

2-Axillary surgery [lymph node dissection]:-
Axillary surgery aims to control axillary metastases if present and to determine disease stage for selection of adjuant therapies such as chemotherapy **[66].**

3-Radiation therapy:-
Radiation therapy is standard of care for women who have undergone lumpectomy or mastectomy surgery. In these cases the purpose of radiation is to reduce the chance that the cancer will recur. Radiation therapy involves using high-energy X-rays or gamma rays that target a tumor or post-surgery tumor site. This radiation is very effective in killing cancer cells that may remain after surgery or recur where the tumor was removed **[67].**

4-Systemic therapy:-
Systemic treatments include chemotherapy, hormonal therapy and immune therapy.

5- Chemotherapy:-

Chemotherapy [cytotoxic drugs] can be given both before and after surgery. Many different types of chemotherapy drugs are used to treat breast cancer. Common types of chemotherapy drug classes include:

1- Anthracyclines include doxorubicin[Adriamycin] and epirubicin[Ellen].

2- Taxanes include paclitaxel [Taxol] and docetaxel [Taxotere].

3- Platinum-based drugs include oxaliplatin[Eloxatin] and carboplatin [Paraplatin]**[68].**

Hormonal treatment. It is used only for patients with estrogen receptor-positive tumors. Different types of hormone therapy work in different ways by:

1- Blocking estrogen receptors in cancer cells [Tamoxifen]

2- Suppressing estrogen production in the body [Aromatase inhibitors]

3- Destroying ovaries, which produce estrogen [Ovarian ablation]. Destroying the ovaries with surgery or radiation or drug treatment to block ovarian production of estrogen is called chemical ovarian ablation **[69].**

6-Targeted therapy:-

In patients whose cancer expresses an overabundance of the HER2 protein, a monoclonal antibody immunotherapy known as trastuzumab.[Herceptin] Is used to block the activity of the HER2 protein in breast cancer cells, slowing their growth. In the advanced cancer setting, trastuzumab use in combination with chemotherapy can both delay cancer growth **[70].**

Conclusion:-

In this survey, we see biomarkers especially principal for the determination growth infection for anticipating tumor drug reactions. An enhanced perception of these potential biomarkers for the early range and prescience of midsection sickness and for foreseeing chemotherapy resistance ought to permit better. Along these lines, it ought to be obligatory however wellbeing couldn't give a hesitation fewer pros amazingly midsection tumor disorder to be mindful of differing customs for dealing with the supportive crises. This especially the condition when there is a need to understand if tumors are of the pivotal or metastatic root. Present this refinement, experts can screen the chromosomal changes found in cells orchestrated in the key tumor site against those found in the optional site.

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