Biomarker is a parameter which is used to measure the progress of disease or the effects of treatment and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. Different types of biomarkers are used in diagnosis as well as prognosis of diseases of cancer. This review focuses on various types of biomarkers and their significance with special reference to cancer diagnosis and prognosis.

Key words: Biomarker, Diagnosis, Lymphocyte, Methylation, Susceptibility.

INTRODUCTION
Cancer cells lump together and form a mass of extra tissue known as a tumor, which continues to grow. As it grows, it may damage and invade nearby tissue. If a cancerous tumor outgrows its birthplace (called the primary cancer site) and moves on to another place (called the secondary cancer site), it's referred to as metastasizing (Silverman, 2014). There are several types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that occurs in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues. Leukemia is a cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of brain and spinal cord. Biomarker is used to refer measurable characteristics that reflect or presence of some disease state which is used as the severity an indicator of a particular disease state or some other physiological state. It can be a substance that is introduced into an organism to examine organ function or other aspects of health (Wagner, 2002; Naylor, 2003). For example, rubidium chloride used as a radioactive isotope to evaluate perfusion of heart muscle. It indicates a change in expression or state of a protein that correlates with the risk or progression of a disease with the susceptibility of the disease to a given treatment. These are characteristic biological properties that can be detected and measured in parts of the body or tissue. They may indicate either normal or diseased processes in the body. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers. It has been used in pre-clinical research and clinical diagnosis for a considerable time. A biomarker is a parameter that can be used to measure the progress of disease or the effects of treatment (Sahu et al 2011). The parameter can be chemical, physical or biological. In molecular terms biomarker is "the subset of markers that might be discovered using genomics, proteomics technologies or imaging technologies. Biomarkers play major roles in medicinal biology. It helps in early diagnosis, disease prevention, drug target identification, drug response etc (Loukopoulos et al 2003).

Types of biomarker
Biomarkers are an objective measure or evaluation of normal biological processes, pathogenic processes, or pharmacological
responses to a therapeutic invention (Table 1).

**Cytogenetic and cytokinetic markers**
Structural and numerical aberrations in chromosomes are classical markers of cancer as the association between chromosomal aberrations and neoplastic transformation has been well established. While deviations from diploid chromosome number leading both to hyper and hypo-diploidy as well as aneuploidy have been noted in malignant tumour. Sister Chromatid exchanges and translocations give rise to structural aberrations that can be easily scored using various banding techniques. Further homogenously stained regions (indicative of gene amplification) are observed in malignant cells that can serve as markers although, the ploidy changes complement the clinico-pathological findings, a weak association between ploidy, histological and clinical staging has been noted in many tumours. Somatic mutations (in reporter genes, oncogenes and tumour suppressor genes) are promising biomarkers for cancer risk as these can capture genetic events that are associated with malignant transformation (Bishop, 1987).

**Genetic biomarkers**
Cancer is a genetic disease initiated by alterations in genes, such as oncogenes and tumor suppressors that regulate cell proliferation, survival and other homeostatic functions. Gain/loss of gene function is predominantly responsible for oncogenic transformation. Several proto-oncogenes get converted into oncogenes (Thor et al 1992).

**Epigenetic biomarkers**
In cancer cells, genes and their functional products are either modified by mutations, or through epigenetic modifications to chromosomes that alter gene-expression patterns. Epigenetic modifications can occur directly through DNA methylation of genes or indirectly by methylation, acetylation, or phosphorylation of histones and other proteins around which DNA is wound to form chromatin (Herman and Baylin, 2003. In recent years, it has become apparent that epigenetic events are potentially responsible for cancer initiation and progression as genetic abnormalities with DNA hypo- and hyper-methylation promoting cancer development. Genomic hypomethylation may lead to both genomic instability and stronger gene expression. Hypermethylation markers used for the detection of both primary and metastatic or recurrent cancer cases.

**Cells as biomarker**
Advanced clinical practice in certain malignancy has effectively used tumour and immune cells where it served as a good biomarker of prognosis. Circulating tumour cells (CTCs): It is powerful biomarker in the field of oncology. The presence of CTCs has been shown to predict survival in patients with metastatic breast cancer at multiple time points throughout the course of therapy. Elevated CTCs at any time during therapy is a harbinger of progression, while elimination of CTCs indicates effectiveness of therapy (Shaffer et al 2007).

**Viral biomarker**
Among viral induced cancers, hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a leading cause of death in developing countries. Risk factors include chronic hepatitis infections mainly due to the endemic hepatitis B virus (HBV) infection, whereas association of hepatitis C virus (HCV) infection is also reported in a small fraction (12-17%) of the HCC cases (Kirk et al 2006). A number of different types of biomarkers have been used to understand the a etiology and progression of HCC. Perhaps, the most well known are the serum/plasma markers of HBV or HCV infection. These markers include analysis of viral DNA or proteins or antibodies produced against the viral proteins.

**Role of biomarkers**

**Prognostic**
These cancer biomarkers help assess the risk of developing a particular cancer and determine prognosis and tissue inhibitor of metalloprotease-1 (TIMP1) this type of type biomarker, gives a better prognosis to the myeloma patients with lower levels of this protein (Ludwig and Weinstein, 2005).

**Diagnostic**
Diagnose the particular type of cancer when pathologists are uneasy to name the specific type of cancer from just looking at the cells.

**Predictive**
Predict the response to cancer drug(s) or treatment(s) in the patient. An example of this is human epidermal growth factor receptor 2 (HER-2) over expression due to an aberrant


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**Metabolic biomarker**

| Glucose metabolism | All cancers, general | Diagnostic, prognostic and therapeutic | Imaging/FDG-PET scan |

**Genetic biomarkers**

| Genetic translocations viz. Philadelphia chromosome, Bcl2 and other gene translocation fusion products | AML, ALL, CML, MDS and Burkitt’s lymphoma | Diagnostic | Bone marrow or peripheral blood/FISH |

| APC gene | Adenocarcinoma, squamous cell carcinoma of the stomach, pancreas, thyroid and ovary | Diagnostic and prognostic | Blood, Tumour sample/ RFLP of chromosome 5q21-22, Methylation status of APC gene |

**Cells as biomarker**

| Circulating tumour cells (CTCs) | Metastatic breast cancer etc. | Diagnostic and prognostic | Blood/Immunocytometry |

| Cancer stem cells (CSCs) | AML, melanoma, brain tumour, breast cancer, prostate cancer | Diagnostic, prognostic and therapeutic | Tumour sample/ Immunocytometry |

Table 1. Cancer biomarkers for diagnosis and prognosis of the disease (Terpos et al 2010)

increase in the HER-2 gene (Ludwig and Weinstein, 2005).

Pharmacodynamics and Pharmacokinetics

Cancer biomarkers under this category help determine the most effective dosage of drug or therapy is needed for that specific person. These biomarkers are another tool aiding the field of personalized medicine and thiopurine methyltransferase (TPMT) gene is example of it. Patients with mutations in gene encoding TPMT are unable to metabolize large amounts of a leukemia drug, mercaptopurine, and this results affects in white blood cell count (Relling et al 1999).

Recurrence

Recurrence biomarkers are used to predict if cancer is likely to come back after treatment, Oncotype DX® breast cancer assay is example of
Significance of biomarkers

Early detection of lung cancer

Lung carcinogenesis is a multistep and multicentric process characterized by the stepwise accumulation of genetic and molecular abnormalities following carcinogen exposure, resulting in selection of clonal cells with uncontrolled growth capacities. Molecular lesions occur in normal looking epithelium in the absence of dysplasia. These have been shown to precede the morphological step of preneoplastic bronchial lesions, which are described as metaplasia, mild dysplasia, moderate dysplasia, severe dysplasia (Esteller et al 1999). These lesions are multiple, reflecting the fact that the carcinogenic process may randomly affect any site in the bronchial tree. The current hypothesis is that molecular characteristics of any individual lesion, with regard to deregulation of cell cycle or apoptosis, might reflect its potential for progression. The accumulation of genetic and molecular abnormalities leads to an uncontrolled growth of clonal cells and an increased ability of these cells to migrate, which characterizes cancer progression, i.e. tumors growth and metastasis.

Mechanisms of genetic and molecular abnormalities

During cellular division, the loss of DNA or chromosomal rearrangement increases with the rate of synthesis and division. Several years ago, using cytogenetic techniques, that deletion of the short arm of chromosome 3 (3p) is very frequent in lung cancer. Like other chromosomal deletions, it corresponds to a site where one or several TSG are present and therefore inactivated (Liu and Tsao, 1993). For a tumor supressor gene previously identified, it is easy to check the deletion on the corresponding chromosomal site.

An increased micronucleus frequency in peripheral blood lymphocytes predicts the risk of cancer in humans

Measurement of micronucleus (MN) frequency in peripheral blood lymphocytes (PBL) is extensively used in molecular epidemiology and cytogenetics to evaluate the presence and extent of chromosomal damage in human populations exposed to genotoxic agents or bearing a susceptible genetic profile. The high reliability and low cost of the MN technique, has contributed to the worldwide success and adoption of this biomarker for in vitro and in vivo studies of genome damage. MN originate from chromosome fragments or whole chromosomes that are not included in the main daughter nuclei during nuclear division. The formation of MN in dividing cells is the result of chromosome breakage due to unrepaired or mis-repaired DNA lesions, or chromosomal segregation due to mitotic malfunction. These events may be induced by oxidative stress, exposure to clastogens or mutagens, genetic defects in cell cycle check point and/or DNA repair genes, as well as deficiencies in nutrients required as co-factors in DNA metabolism and chromosome segregation machinery (Fenech, 2002). The presence of an association between MN induction and cancer development is supported by: (i) the high frequency of this biomarker in untreated cancer patients and in subjects affected by cancer-prone congenital diseases, e.g. Bloom syndrome or ataxia telangiectasia (ii) the presence of elevated MN frequencies in oral mucosa, used as a surrogate biomarker of cancer in clinical chemoprevention trials (iii) the correlation existing between genotoxic MN-inducing agents and carcinogenicity, e.g. ionizing and ultraviolet radiation (iv) the inverse correlation between MN frequency and the blood concentration and/or dietary intake of certain micronutrients associated with reduced cancer risk, such as folate, calcium, vitamin E and nicotinic acid. The possible association of lymphocyte MN frequency with cancer risk has earlier been examined in Swedish and Italian cohorts.

Genetic susceptibility to lung cancer

People differ in their susceptibility to disease. Lung cancer epitomizes this concept. More than 80% of lung cancers are attributed to tobacco (Tlsty et al 1995). Genetic instability, which drives tumor genesis, is itself fuelled by DNA damage and by errors made by the DNA repair machinery. DNA repair is a ubiquitous defense mechanism that is critical to maintaining the integrity of the genome and repairing the damage from exposure to exogenous environmental xenobiotics, as well as to endogenous damage (e.g. from oxidative metabolism) or spontaneous disintegration of chemical bonds in DNA. The types of assays...
include: (a) those using a chemical or physical mutagen challenge (such as the mutagen sensitivity, Comet, and induced adduct assays); (b) unscheduled DNA synthesis; and (c) measuring cellular ability to remove adducts from plasmids transfected into lymphocyte cultures in vitro by expression of damaged reporter genes (the host-cell reactivation assay). There are many assays that measure the efficiency of the multiple steps of excision repair individually; the ability to test the whole pathway is often needed for population studies, in which time, cost, and repeatability of measurements are major concerns. Therefore, measuring the expression level of damaged reporter genes using host-cell reactivation is the assay of choice. This assay uses undamaged cells, is relatively fast, and is an objective way of measuring intrinsic cellular repair. In the assay, lymphocytes are transfected with damaged nonreplicating recombinant plasmid harboring a CAT gene.

**Aberrant methylation of p16INK4a as an early event in lung cancer and a potential biomarker for early diagnosis**

The p16INK4a (p16) tumor suppressor gene that maps to chromosome band 9p21 is inactivated in 70% of cell lines derived from all histologic types of human non small cell lung cancers (NSCLCs) predominantly through homozygous deletion or in association with aberrant promoter region hypermethylation. These inactivating events are conserved across species with homozygous deletion and aberrant methylation accounting for loss of p16 expression in 40% and 45% respectively of cell lines derived from rat lung tumors (Crowell et al. 1996). Moreover, the methylated phenotype seen in the rat cell lines showed an absolute correlation with the detection of methylation in primary tumors and the aberrant promoter region methylation was also detected in four of eight primary tumors from which the derived cell line had homozygous deletion of p16. Thus, the methylation change may precede genetic instability within the CpG island of this gene. Several genetic abnormalities frequently present in human lung cancer have now been found throughout the respiratory tract of smokers (Wistuba et al. 1997). These include allelic loss, but not homozygous deletion, involving 9p21 in remalignant lesions from cancer and cancer-free patients. This finding suggests that inactivation of the p16 gene by aberrant methylation could represent a critical step in the genesis of SCLC by allowing the uncontrolled clonal expansion of some of these premalignant lesions to cancer.

**Urokinase plasminogen activator receptor: Prognostic biomarker for endometrial cancer**

Endometrial cancer is the most common malignancy of the female genital tract in the United States. More than 36,100 new cases of endometrial cancer were diagnosed in the year 2000 with more than 6,500 deaths reported in the same year. Clinical parameters such as the stage of disease, nuclear grade, histologic subtype, and tumor size seem to correlate without come of disease. A prognostic marker needs to be an independent factor that not only guides treatment but also has an impact on patient survival. These criteria are rarely satisfied because most candidate prognostic markers fail to distinguish between tumors that require adjuvant treatment and those that do not. For example, tumor suppressor gene(s) (e.g., p53), oncogene(s) (e.g., HER-2 neu, K-ras), and DNA repair gene(s) (e.g., hMLH1) mutation have played a role in endometrial cancer (Sasaki et al. 1993; Esteller et al. 1999). Recently, it was demonstrated that urokinasesominogen activator receptor (UPAR) mRNA levels correlated with the invasive potential of endometrial carcinomas and showed a 33-fold increase in UPAR mRNA levels in advanced clinical stage endometrial tumors compared with normal endometrial tissue.

Our goal, ultimately, was to determine whether UPAR protein could be used as a candidate prognostic marker for patients with cancer of the endometrium.

**Role of RAB GTPases in cancer and human disease**

Decreasing cancer is caused by abnormalities in DNA sequence, copy number, rearrangements, or expression. The accumulation of multiple changes in critical genes within a single cell is required to escape from normal controls on cell growth and proliferation, allowing development into a clinically evident tumor. Large-scale profiling of gene expression and genomic alterations has revealed multiple differences between normal and malignant cells, specific genetic and cellular changes that occur at each stage of tumor progression. Array comparative genomic hybridization provides a robust, sensitive, and high-resolution approach to the identification of regions of DNA copy number
increase and decrease in tumors. These copy number aberrations are selected during tumorigenesis (Gray et al 2003). Multiple chromosomal amplifications implicated in the pathophysiology of ovarian and breast carcinomas have been detected. The identification of the candidate genes driving the development of the DNA copy number aberrations in cancer has progressed at a slow rate. However, new technologies are likely to increase the pace.

**Issues affecting molecular detection, screening and treatment**

Development of biomarkers for cancer screening, detection and treatment involves both biological and economic challenges. Most detection methods in use to date identify fully developed cancer. Although a screening test might detect cancer at the preclinical stage, it could fail to detect micrometastasis and thereby limit the benefit of early detection and treatment. Another problem is that in many organs, for example, prostate or colon, pre-neoplastic lesions are much more common than aggressive cancers and only 10% or less develop into a malignant tumor. Cancer is a heterogeneous disease, meaning that the disease itself is composed of many biologically different phenotypes with varied responses to intervention, including screening and treatment (Manne et al 1988).

**Bias in biomarker discovery**

Cancer therapy is commonly evaluated through a well controlled randomized trial that addresses issues related to bias, heterogeneity and other confounding factors, such as age, sex, hormonal status, and so on. By contrast, research studies on biomarkers are usually conducted using observational epidemiology or clinical epidemiology rules that are less well defined. However, the rules of clinical epidemiology of diagnostics and prognosis can improve the evaluation of molecular markers, especially for handling heterogeneity, complexity and bias. Recently, several sophisticated genomic and proteomic analyses of tumor cells have provided useful information on molecular signatures for discriminating cancer cells from non-cancerous cells. However, it would be an insurmountable task to conduct a clinical trial for each promising biomarker, a task that would be prohibitively expensive and time-consuming. One of the major problems with high-dimensional data derived from high throughput genomic and proteomic technologies is over fitting of the data when there are large numbers of potential predictors among a small number of outcome events.

**Development and evaluation of biomarker**

Because of tumor heterogeneity and other biases that might be inherently imbedded with biomarker discovery and evaluation processes, it is important that the discovery of biomarkers should proceed in a systematic manner. Unlike a clinical trial design in which there are three phases (Phase I, Phase II and Phase III), research on biomarkers has largely been guided by intuition and experience. In 2002, the National Cancer Institute’s Early Detection Research Network developed a five-phase approach to systematic discovery and evaluation of biomarkers. In general, biomarker development should follow an orderly process wherein one proceeds to the next phase only after meeting pre-specified criteria for the current phase.

- **Phase 1:** Biomarkers are discovered through knowledge-based gene selection, gene expression profiling or protein profiling to distinguish cancer and normal samples.
- **Phase II:** The clinical assay could be a protein-, RNA-, DNA- or a cell-based technique, including ELISA, protein profiles from MS phenotypic expression profiles, gene arrays, antibody arrays or quantitative PCR. The assay is evaluated for its clinical performance.
- **Phase III & Phase IV:** A positive test triggers a definitive diagnostic procedure, often invasive and could lead to increased economic healthcare.
- **Phase V:** Evaluates the overall benefits and risks of the new diagnostic test on screened population (Kelloff et al 2004).

**Biomarker in drug development**

The major challenges in cancer drug development are discriminate responses, efficacy and toxic side effects. The pharmaceutical industry, drug policy makers and administrator are constantly looking for novel pharmacogenomics and/or pharmcoproteomic studies that might identify potential molecular biomarkers to help solve this problems (Wagner, 2002). To increase the efficiency and quality of drug discovery, biomarkers could be used. Biomarkers can be useful for in vitro evaluations of hundreds of candidates that are typically screened during the drug development process. Biomarkers can also be used in measuring drug toxicity and pharmacokinetics in Phase II clinical
trials. Most Phase IIb and Phase III trials are conducted using reduction in mortality or disease-free survival as the endpoint, and studies are usually large (several thousand patients) and long (more than 10 years large (several thousand patients) and long (more than 10 years).

Recent advances in biomarker for cancer diagnosis and development
Thousands of biomarkers have been discovered to be potential biomarkers for cancer diagnosis and detection. Biomarkers must distinguish between people with cancer and those without. In cancer biomarker testing, the sensitivity of a biomarker refers to the proportion of case subjects (individuals with confirmed disease) who test positive for the biomarker, (individuals without disease) who test negative for the biomarker. An ideal biomarker test would have 100% sensitivity and specificity; in other words, very one with cancer would have a positive test and everyone without cancer would have a negative test. The lower sensitivity, the more often that individuals with cancer will not be detected, and the lower the specificity, the more often someone without cancer will test positive (Wagner et al 2004). None of the current available biomarkers achieve 100% sensitivity and specificity. For example, prostate specific antigen (PSA), currently the best overall serum biomarker for prostate cancer, has high sensitivity (greater than 90%) but low specificity (~25%), which results in many men having biopsies when they do not have detectable prostate cancer (Gillatt and Reynard, 1995). The serum tumor biomarker for breast cancer CA15.3 has only 23% sensitivity and 69% specificity and is only useful in monitoring therapy for advanced breast cancer or recurrence.

Recent advances in drug development based on molecular biomarker
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 are proven in both experimental and clinical conditions. A novel approaches are intended to identify individualized patient benefits of therapies, minimize the risk of toxicity and reduce the cost of treatment. The biggest challenge for researchers and clinicians today is which type of biomarker to use across the wide spectrum of disease processes. In cancer, genomic studies are valuable because every cancer cell shows some degree of genetic damage, which might not be present in normal cells of the body. However, proteins, peptides or metabolites are abundant, easily accessible in body fluids, such as blood, urine, cerebrospinal fluid and secretions, and show promise for measuring outcomes and studying changes in disease state. Another challenge in characterizing biomarkers is the complexity of the expression profile of potential markers in benign conditions close to the disease phenotypes. The evolving trend is the usage of patterns of markers instead of a single marker (Manne et al 2005).

Future aspects of biomarker
Age of technology future is bright for biomarker. Institutes are working on the Human Genome Project and Cancer Genome Atlas, early results from collaborative biomarker discovery projects should be released into the public domain to encourage further detection of cancer there is possibility that can detect cancer before the tumor formation. Collaboration with pharmaceutical industries is essential because experimental anticancer drugs are an essential reagent for biomarker discovery experiments. It is time to establish an associative approach using a public-private partnership model to solve the cancer biomarker problem. There are two major approaches to molecular marker discovery. In the high throughput strategies thousands of contenders are screened simultaneously. In the traditional hypothesis driven approach, interactions between molecules known to be important to pancreas cancer development are studied to identify novel molecules and pathways. The marker currently used for Cancer Prostate (CaP) detection is an increase in serum prostate specific antigen (PSA). PSA test may give false positive or negative information and does not allow the differentiation of benign prostate hyperplasia (BPH), non-aggressive CaP and aggressive CaP. Tears are a unique source of body fluid and contain proteins, peptides, mucins and lipids, which is useful for studying clinical proteomics Early diagnosis of cancer needs focus on biomarkers identification. Approach may be the study of signaling system of pathways related with cancer in our body (Karley et al 2011).
CONCLUSION
Cancer cells lump together and form a mass of extra tissue known as a tumor, which continues to grow. Biomarker is used to refer to measurable characteristics that reflect or present of some disease state which is used as an indicator of the severity a particular disease state or some other physiological state. It indicates a change in expression or state of a protein that correlates with the risk or progression of a disease with the susceptibility of the disease to a given treatment. It helps in early diagnosis, disease prevention, drug target identification, drug response etc. The sensitivity of a biomarker refers to the proportion of case subjects (individuals with confirmed disease) who test positive for the biomarker (individuals without disease) who test negative for the biomarker. Development of biomarkers for cancer screening, detection and treatment involves both biological and economic challenges. These novel approaches are intended to identify individualized patient benefits of therapies, minimize the risk of toxicity and reduce the cost of treatment. The biggest challenge for researchers and clinicians today is which type of biomarker to use across the wide spectrum of disease processes. To increase the efficiency and quality of drug discovery, biomarkers could be used. Biomarkers can be useful for in vitro evaluations during the drug development process. Biomarkers can also be used in measuring drug toxicity.

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