معهد الهندسة الوراثية والتقانات الاحيائية
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Cancer biomarkers

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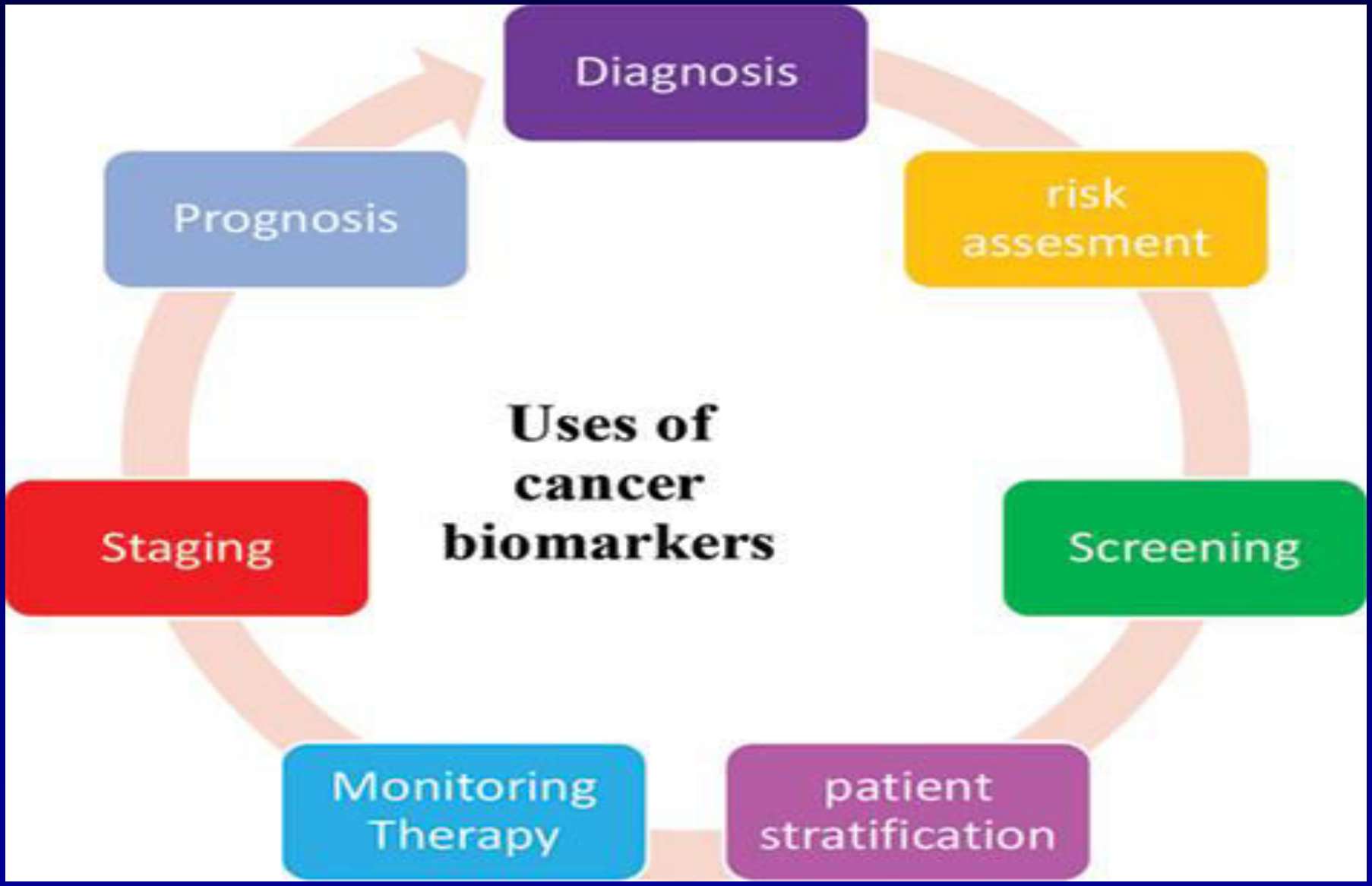
Cancer biomarkers

Cancer biomarkers (CB) are biomolecules produced either by the tumor cells or by other cells of the body in response to the tumor, Cancer biomarkers could be used as screening/early detection tool of cancer, diagnostic, prognostic, or predictor for the overall outcome of a patient.

The medical usage of new biomarker is considered to play an important role in reforming biomedical science research,

Moreover, cancer biomarkers may identify subpopulations of patients who are most likely to respond to a given therapy .

Biomarkers can be genes, gene products, specific cells, molecules, enzymes, or hormones which can be detected in blood, urine, tissues, or other body fluid .



Clinical uses of cancer biomarkers.

Types of Biomarkers

The biomarkers used today in medicine and research generally fall into several categories.

1- Molecular or biochemical biomarkers

Molecular or biochemical markers are biological molecules found in body fluids or tissues. In cancer, molecular biomarkers are often genes or gene products such as proteins.

An example is prostate specific antigen. Prostate specific antigen is a protein produced by prostate cells that is normally found in low levels in the blood of men. Increased levels of prostate specific antigen are used as a diagnostic biomarker for prostate cancer.

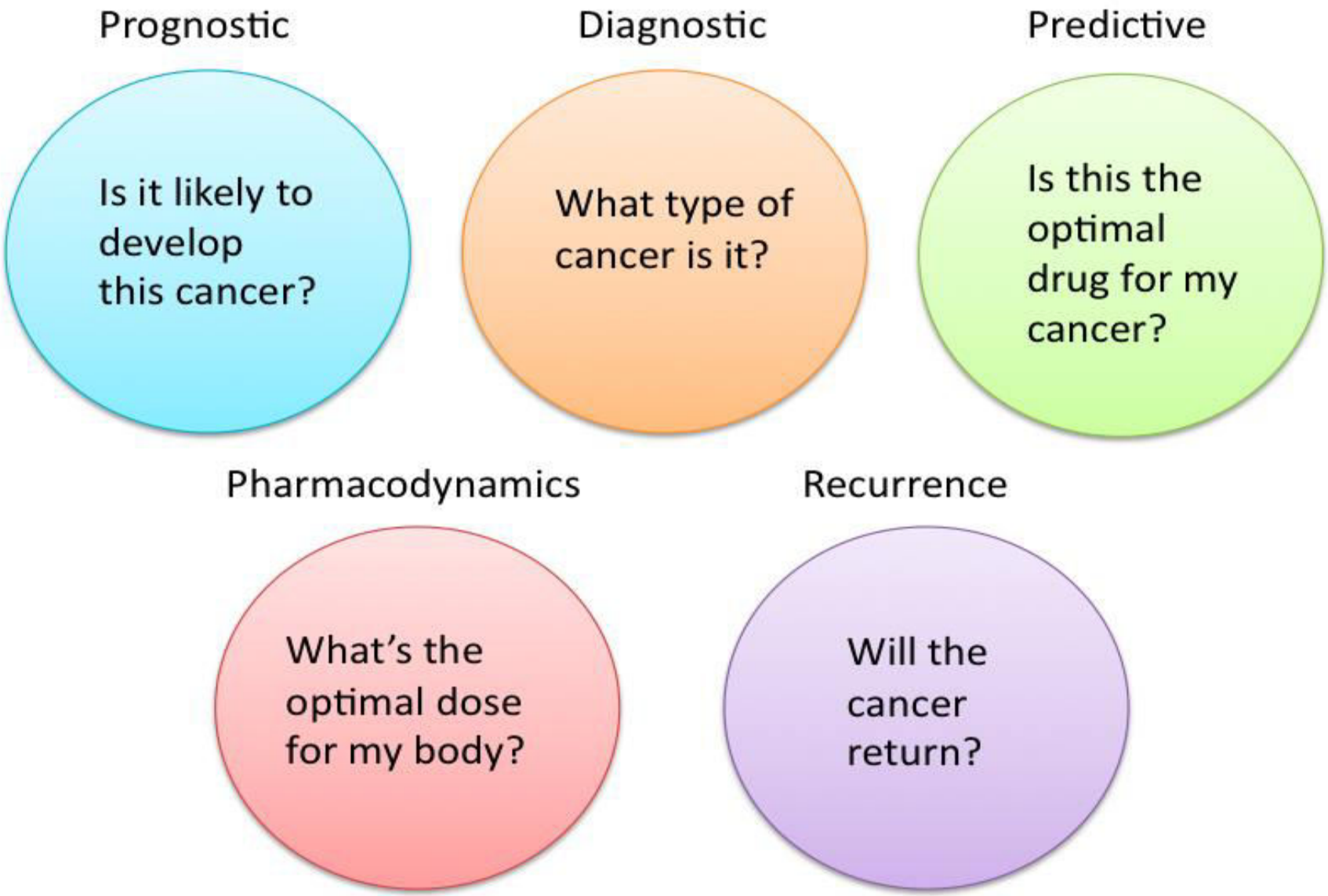
2- Physiologic biomarkers

Physiologic biomarkers are those that have to do with the functional processes in the body. For example blood flow in brain areas affected by stroke is being investigated as a potential indicator of treatment success.

3- Anatomic biomarkers

Anatomic biomarkers are those that have to do with the structure of an organism and the relation of its parts. Anatomic biomarkers include the structure of various organs such as the brain or liver. For example, the size of certain brain structures in relation to one another is a biomarker for a movement disorder known as Huntington disease.

Questions that can be answered by cancer biomarkers



What is the purpose of biomarkers?

Biomarkers may have at least one of several purposes:

(i) to help diagnose a condition, perhaps before the cancer is detectable by conventional methods; this is known as a diagnostic biomarker. screening CB should be able to detect cancer in an early stage and consequently will result in increase of survival rate and decrease complications

(iii) to help in therapeutic monitoring/follow-up/evidence of metastasis or recurrence Therapeutic monitoring is the most common applications of CB markers in medicine.

Clinically useful biomarkers usually swing in accordance with tumor behavior, size, or burden changes that are detect by increase in levels of CB with progressive disease, decrease with remission, and do not change significantly with stable disease.

Recurrence of cancer may be detected biochemically via rise in CB levels even before appearance of any clinical or radiological evidence of cancer recurrence.

The purpose of biomarkers

Role of Biomarker	Description of Use
Diagnostic	To help diagnose a cancer, perhaps before it is detectable by conventional methods
Prognostic	To predict how aggressive the disease process is
Predictive	To help identify which patients will respond to which drugs

The characteristic features of an ideal biomarker should be considered for selection of diagnostic biomarker

- **High clinical sensitivity:** produced by all patients with that specific cancer .
- **High clinical specificity:** low false negative rate .
- **Organ or tissue specific**.
- **Proportional to** tumor volume or disease progression. speed of growth: Quantifying the
- change of total tumor volume in whole-body
- **Short half-life**: reflecting quickly any early changes in tumor for monitoring of therapy.
- **Present at low levels in the serum of healthy individuals and those with benign disease**.
- **Sharply discriminating metastasis.**
- **Inexpensive or low coasting method.**
- **Obtained in noninvasive manner detected in serum ,body fluid ,or in easily accessible tissue**

mechanisms for the production of cancer biomarkers

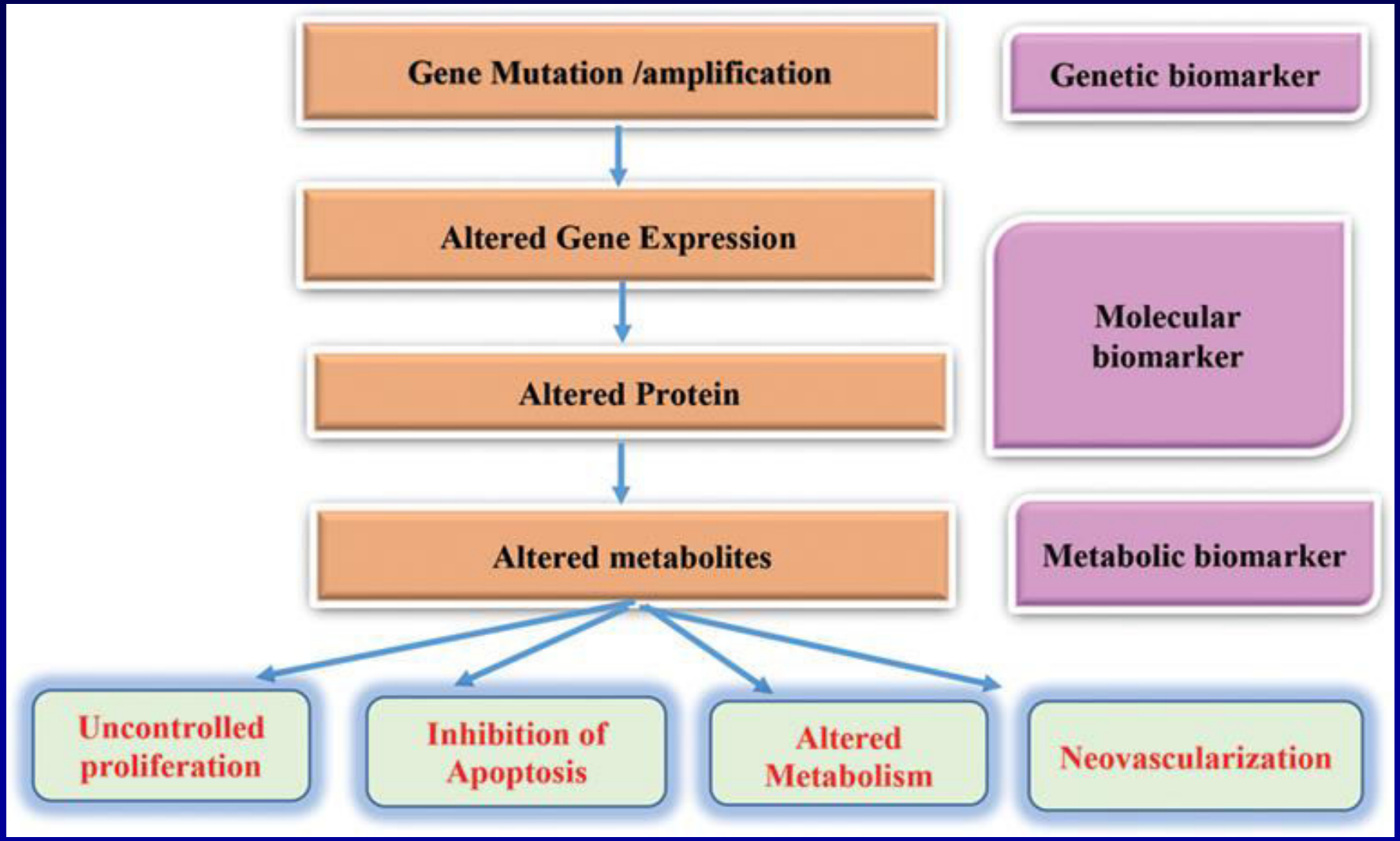
Cancer is a multifactorial cluster of diseases reflecting fundamental abnormality involving uncontrolled cell growth and proliferation alternating the normal cell behavior. Molecular mechanisms exhibit alterations in the expression of multiple genes mostly includes:

(proto) oncogenes, tumor suppressor genes, DNA repair genes. that contribute to the development of cancer with a state of dysregulation of cell proliferation events.

Genetic alterations of cancer cells, as point mutation, gene rearrangement or amplifications, and subsequent disturbances of cell division and proliferation will be manifested by release of biomarkers of such changes in majority of patients with a specific type of cancer.

One of the major challenges for oncology research is to establish the definite relationship between cancer biomarkers and cancer pathology, as well as, to detect cancer in early stage beside the development of targeted therapies targeting the exact altered gene or cellular process .

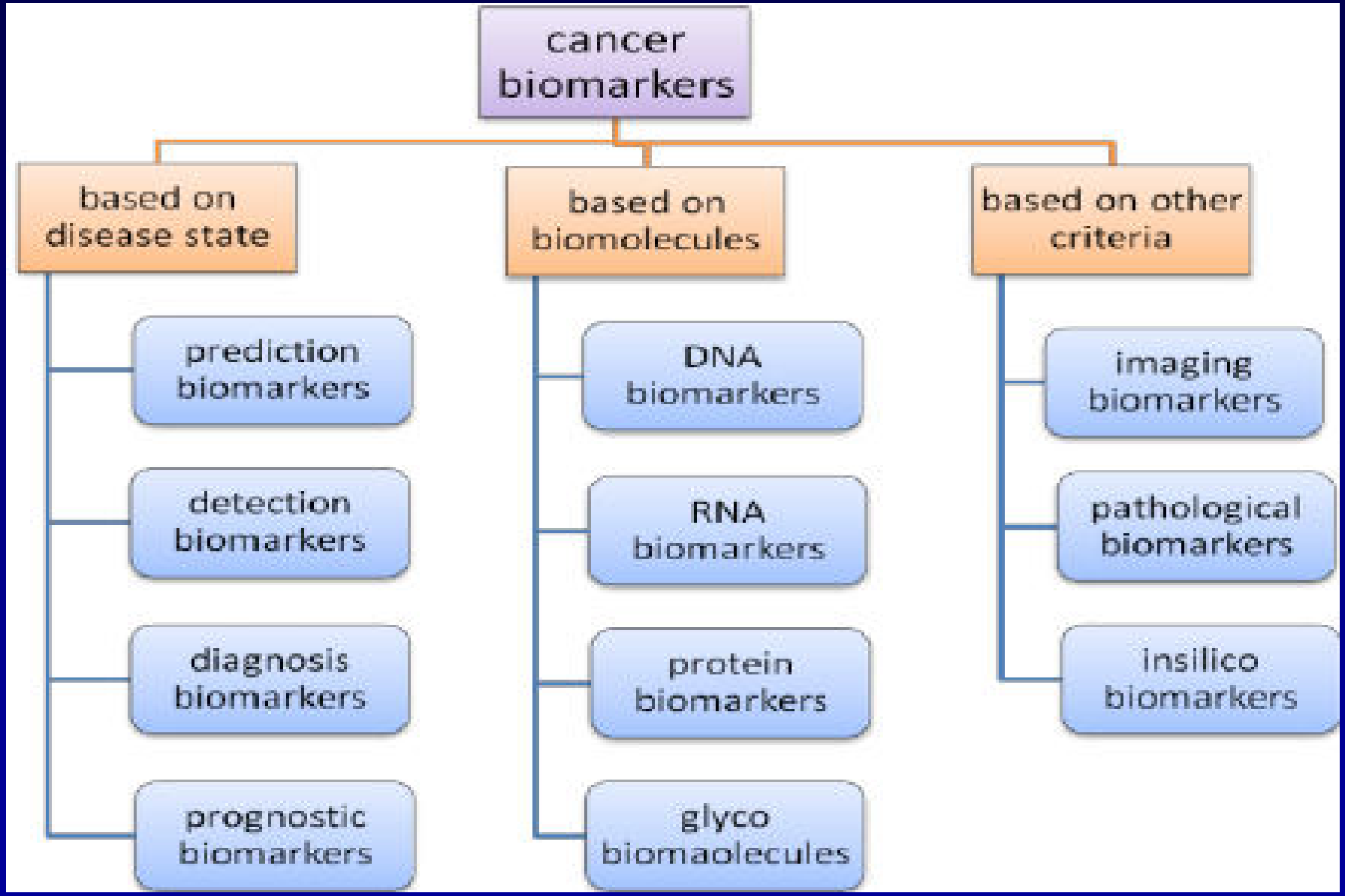
Identification of biomarkers in the process of carcinogenesis



Current cancer biomarkers and uses in cancer research

Cancer biomarker	cancer type	Application/uses
Prostate-specific antigen (PSA)	Prostate/BPH	Screening, diagnosis and monitoring therapy
Carbohydrate antigen 125 (CA125)	Ovarian	Diagnosis, prognosis, detecting recurrence and monitoring therapy
Carcinoembryonic antigen (CEA)	Colorectal/hepatic	Monitoring therapy Prognosis Detecting recurrence Screening for hepatic metastases
Carbohydrate antigen 15.3 (CA 15-3)	Breast	Monitoring therapy
Estrogen, progesterone receptors (ER and PgR)	Breast	Select patients for endocrine therapy
Carbohydrate antigen 27.29 (CA27.29)	Breast	Monitoring
Human chorionic gonadotropin-β (HCG-β)	Testicular	Diagnosis Staging Detecting recurrence Monitoring therapy
Alfa-fetoprotein	Hepatocellular carcinoma	Diagnosis Detecting recurrence Monitoring therapy
Thyroglobulin	Thyroid	Monitoring
CA 19-9	Pancreatic	Monitoring therapy
Nuclear matrix protein 22 (NMP-22)	Bladder	Screening, monitoring and prognosis

Classification of Biomarkers



Cancer biomarkers can be grouped according to genomic state

1- Molecular genetic markers

DNA marker:

Cancer is a genetic disorder with a collection of mutations in genes , that is typically found in two classes of genes:
cancer-promoting oncogenes and cancer preventing tumor suppressor genes .
Such mutations can cause gene to either lost or gained function .

Oncogenes and tumor suppressor genes are regulatory genes which encode proteins that are checkpoints of the cell cycle and also have an important role for maintaining in the entryway to terminal differentiation and cell death

2- mRNA marker:

Globally, perspective of the mRNA expression forms and deregulated pathways may give a more exact cancer picture including its clinical behavior .

Lots of expression profiling researches had suggested the mRNA expression potential as a model to separate between histologic subtypes of cancer cells, such as clear cell, papillary and chromophobe in renal cell carcinoma [RCC] .

Some of the techniques employed to determine tumor biomarkers at the level of mRNA expression include quantitative reverse transcription polymerase chain reaction .

3- Protein marker:

Proteomics of cancer includes detail on all process of biology that happens in cancer cells . Cancer cells produce some macromolecules and many proteins into the extra-cellular fluid through releasing that could also serve as markers .

Some of these outputs can finish up in the bloodstream and thus serve as potential biomarkers of serum .

Few crucial antigens of cancer are served as diagnostic and prognostic cancer biomarkers such as prostate specific antigen [PSA], alpha-fetoprotein [AFP] and cancer antigen 125 .

Epigenetic markers

DNA methylation marker :

Existence of epigenetic dysregulation is progressively recognized as a cancer hallmark . Accumulating data in the last 10 years suggests that not only genetic alterations but also changes of epigenetic play important roles in cancer progression and development .

Epigenetic regulation is generally organized at the level of DNA [post-replicative methylation], protein [histone modifications] and RNA [RNA interference] .

Non-coding RNA markers:

A Non-coding RNA [ncRNA] is transcribed from primary DNA sequence however not changed over into proteins, that is a functional RNA molecule .

Epigenetic related ncRNAs can be divided into two main groups;

The short ncRNAs and the long ncRNAs.

In general, ncRNAs function to regulate gene expression at the transcriptional and posttranscriptional level .

Both major groups are shown to play a role in DNA methylation targeting, heterochromatin formation, histone modification, and gene silencing.

Short non-coding RNA markers:

Three major classes of short non-coding RNAs are :

microRNAs [miRNAs],
short interfering RNAs [siRNAs],
piwi-interacting RNAs [piRNAs].

MiRNAs are short 18- 24 nucleotides, non-coding RNA sequences, that regulate a wide array of biological processes including carcinogenesis. MiRNAs control gene expression via translational regulation and regulate expression of target gene by corrupting mRNA or suppressing its translation .

Different evidences have demonstrated that miRNA expressions dnysregulated in human cancer through various mechanisms, including amplification or deletion of miRNA genes, abnormal transcriptional of miRNAs is a biomarkers for human cancer diagnosis, prognosis and therapeutic response .

Long non-coding RNA marker :

. lncRNAs are non-protein-coding RNA molecules with a sequence longer than 200 nucleotides . Different evidence indicated that lncRNAs are an important in the genome regulatory network and work via diverse mechanisms , including chromatin modification, transcriptional regulation, and posttranscriptional regulation .

lncRNAs play important roles in Cancer biological processes, such as increasing cell proliferation, migration, and invasion abilities,

Multiple tumor-related lncRNAs have been found in cell lines, tissues, and body fluid of cancer patients. Therefore, these molecules are considered as potential molecular biomarker for cancer diagnosis, prognosis prediction, and therapeutic targets

Histone modification markers:

Recently, it has become more apparent that histone alterations are key players in the chromatin dynamics and states regulation as well as in expression of gene .

modifications of histones have been linked to deregulated expression of many genes with important roles in cancer development and progression.

Modifications of histones is important regulators that can control cellular differentiation, involvement in the different stages of tumorigenesis , proliferation and malignancy processes.

existence of histone alterations is a potential biomarkers of disease prognosis and progression .

Cancer Biomarker Based on Genetics

Cytogenetic markers

Human cancer cytogenetic is the study of chromosomal rearrangements and numerical abnormalities in malignant tissue, hundreds of common chromosomal aberrations have been observed in various tumor .

Because these cytogenetic aberrations provide diagnostic, prognostic, and treatment-related information for the associated cancers, they are considered biomarkers for cancer disease. .

increasing number of Chromosomal aberrations is found to be related with specific diseases or subtypes of cancers .

In acute myeloid leukaemia (AML), cytogenetic abnormalities serve as prognostic biomarkers for risk categorisation. Inversions in chromosome 16 as well as translocations between chromosomes 8 and 21 and chromosomes 15 and 17 are associated with a favorable prognosis,

while deletions in chromosomes 5 and 7 are associated with an unfavorable prognosis.

Recently performed studies show that cytogenetic is important to understanding carcinogenesis because it is closely linked to mutations and changes in chromosomal structure .