Importance of Biomarkers In Diagnosis of Various Diseases- Review article

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ABSTRACT

Biomarkers provide a dynamic and powerful approach to understand the spectrum of various diseases with applications in observational and analytic epidemiology, randomised clinical trials, screening and diagnosis and prognosis. In the recent years knowledge about biomarkers has increased tremendously providing great opportunities for improving the management of patients by enhancing the efficacy of detection and efficacy of treatment. This review provides a brief account on various biomarkers for diagnosis, prognosis and therapeutic purposes, which include markers already in clinical practice as well as various upcoming biomarkers.

Keywords: Biomarkers, efficacy, therapeutic outcome, clinical parameters, epidemiology.

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INTRODUCTION

Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human disease. The application of biomarkers in the diagnosis and management of cardiovascular disease, infections, immunological and genetic disorders, and cancer are well known[1].

Biological markers (biomarkers) have been defined by Hulka and colleagues1 as "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids." More recently,the definition has been broadened to includebiological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [2].

Types of biomarkers

Biomarkers have been classified by Perera and Weinstein[1],based on the sequence of events from exposure to disease.
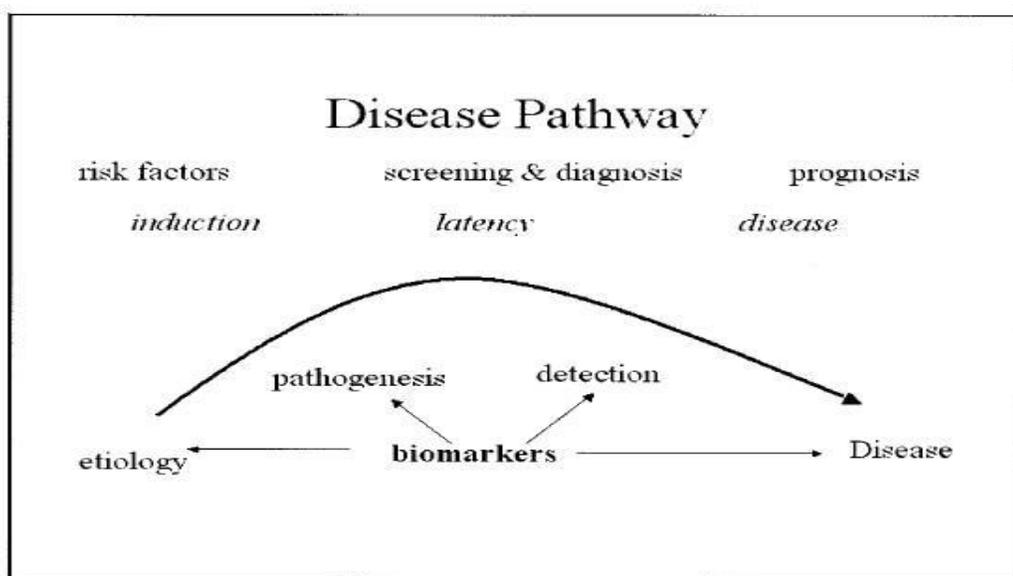

Figure 1: Disease pathway and potential impact of biomarkers

Capabilities of Biomarkers:

- Delineation of events between exposure and disease
- Establishment of dose–response
- Identification of early events in the natural history
- Identification of mechanisms by which exposure and disease are related
- Reduction in misclassification of exposures or risk factors and disease
- Establishment of variability and effect modification

- Enhanced individual and group risk assessments [3].

Advantages:

- Objective assessment

- Precision of measurement

- Reliable; validity can be established

- Less biased than questionnaires

- Disease mechanisms often studied

- Homogeneity of risk or disease.

Disadvantages:

- Timing is critical

- Expensive (costs for analyses)

- Storage (longevity of samples)

- Laboratory errors

- Normal range difficult to establish

- Ethical responsibility [4].

DIFFERENT TYPES OF BIOMARKERS USED FOR DIAGNOSIS OF DISEASES:

Cancer:

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [5].

Classification:

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

Carcinoma:

Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.

Sarcoma:

Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow.

Lymphoma and leukemia:

These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.

Germ cell tumor:

Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue.[6]

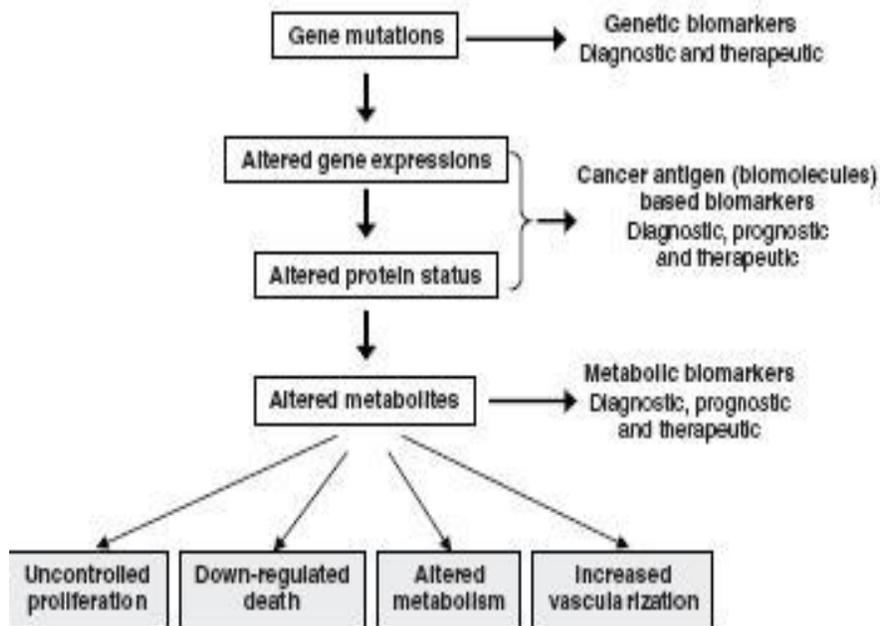**The Process Of Carcinogenesis [7] :**

Figure 2:The process of carcinogenesis, showing opportunities of identifying biomarkers.

Table 1: Cancer antigen (biomolecules) based biomarkers [7]:

Biomarker	Tumour	Application	Sample type/method of detection
Prostrate specific antigen (PSA)	Prostate cancer	Diagnostic and prognostic	Serum/ Immunoassay
Alpha-foetoprotein (AFP)	Hepatocellular carcinomas (HCC)	Diagnostic and prognostic	Serum/ Immunoassay
Cancer antigen 125 (CA125)	Ovarian cancersFallopian tube cancer	Diagnostic and prognostic	Serum/ Immunoassay
Cancer antigen 15-3 (CA15-3)	Breast cancer	Diagnostic and prognostic	Serum/ ELISA,Lymph node/ IHC,Bone marrow/ IHC
Cancer antigen 19-9 (CA 19-9)	Pancreatic cancerBladder cancer	Diagnostic and prognostic	Serum/ ELISA,Urine/ ELISA
BRCA-1, BRCA-2	Breast cancer	Diagnostic	Tumour samples/ RT-PCR
Carcinoembryonic antigen (CEA)	Colorectal cancer	Diagnostic and prognostic	Serum/ ELISA
Human chorionic gonadotrophin (Hcg)	Germ cell tumours (ovarian, testicular)	Diagnostic	Serum/ ELISA

Table 2: Metabolic biomarkers:

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

Table 3: 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

Table 4: 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

Chronic kidney disease:

Chronic kidney disease is the slow loss of kidney function over time. The main job of the kidneys is to remove wastes and excess water from the body [8].

Table 5: GFR values for Various Stages of CKD

CKD Stage	GFR level (mL/min/1.73 m2)
Stage 1	≥ 90
Stage2	60 – 89
Stage 3	30 – 59
Stage 4	15 – 29
Stage 5	< 15

Risk factors:

The most common recognized cause of CKD is diabetes mellitus**.** Others include idiopathic (i.e. unknown cause, often associated with small kidneys on renal ultrasound), hypertension, glomerulonephritis [9].

Table 6: Events and their Bioamarkers

Events	Biomarkers
Kidney function (GFR)	Cystatin C, Beta Trace protein
Tubulointestitial injury	NGAL, KIM-1, NAG, L-FABP
Glomerular injury	Prodocin, nephrin, podocalyxin
Endothelial dysfunction	ADMA
Oxidative stress	OX-LDL, AOPP,TBARS, Plasma and urinary F_2- isoprostanes, MDA, Protein reduced thiols, TAS, Protein carbonyls, AGE, Urinary 8-hydroxydeoxy guanosine, 4-hydroxy-nonenal, antioxidant enzyme activities (e.g.,superoxide dismutase, glutathione peroxidase, catalase), GGT
Inflammation	CRP and hs-CRP, PTX3, sTNFrii, IL-18, Tenascin,TIMP-1
Fibrosis	TGF-b1
Cardiovascular dysfunction	ANP, BNP and NT-proBNP, cTnT, Adrenomedullin
Metabolic disorders	FGF-23, Adiponectin, ApoA-IV

Abbreviations: ADMA, asymmetric dimethylarginine; AGE, advanced glycation end product; ANP, atrial natriuretic peptide; AOPP, advanced oxidation protein products; ApoA-IV, apolipoprotein A-IV; BNP, brain natriuretic peptide; CRP, C-reactive protein; cTnT, cardiac troponin T; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; GGT, g glutamyltransferase; hs-CRP, high-sensitivity-CRP; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; MDA, malondialdehyde; NAG, N-acetyl-b-O-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal brain natriuretic peptide; Ox-LDL, oxidized low-density lipoproteins; PTX3, pentraxin 3;

sTNFrii, soluble tumor necrosis factor receptor II; TAS, total antioxidant status; TBARS, thiobarbituric acid reactive substances; TGF-b1, transforming growth factor-b1; TIMP-1, tissue inhibitor of metalloproteinases-1[10].

BIOMARKERS IN BRAIN DISEASE:

Brain disease is any disease of the brain or nervous system like brain disorder, encephalopathy and having 33 types. These are categorized into 3 major groups. They are

- Nervous disorder
- Neurological disease
- Neurological disorder [11].

Table 7: Brain biomarkers in multi-site studies [11]:

Consortia	Disorder	Protocols	Data analysis
BioMS-eu	MS	CSF collection, processing and bio banking	Standardized reporting
AddNeuroMed	AD, MCI	MRI acquisition MRI quality control	Automated analysis techniques
Parkinson's ProgressionMarkers Initiative	PD	CSF and plasma collection and biobanking, MRI, DTI acquisition	Standardized data collection and processing

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson's disease; DTI, diffusion tensor imaging.

RHEUMATOID ARTHRITIS:

Rheumatoid arthritis (RA) is an inflammatory arthritis that affects nearly 1% of the world's adults. It is characterized by symmetric polyarticular inflammation of the synovium, typically of the small joints of the hands (MCP and PIP), wrists and feet. This inflammation results in pain and stiffness, and can lead to progressive joint damage resulting in deformities and loss of function [12].

Etiology:

- Half of the risk for RA is believed to be genetic [13].
- It is strongly associated with the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DRB1 (most specifically the shared epitope alleles, including *0401 and born 0404), and the genes PTPN22 and PADI4—hence family history is an important risk factor.[14,15]
- Inheriting the PTPN22 gene has been shown to double a person's susceptibility to RA.
- PADI4 has been identified as a major risk factor in people of Asian descent, but not in those of European descent [16].

- First-degree relatives prevalence rate is 2–3% and disease genetic concordance in monozygotic twins is approximately 15–20% [17,18].

Table 8:Biomarkers In Rhuematoid Arthritis Diagnosis [19]:

Biomarker	Biomarker category	Primary role
VCAM-I	Adheshion molecules	Cellular influx and tissue expansion
EGF,VEGF-A	Growth factors	Cellular influx and tissue expansion
IL6,TNF-R1	Cytokine related protein	Local inflammation and destruction
MMP1,MMP3	Matrix,metalloproteinases	Cartilage degradation and joint damage
YKL-40	Skeletal related proteins	Stromal activity and regulation
Leptin	hormones	Systemic inflammatory response
SAA,CRP	Acute phase proteins	Systemic inflammatory response

CONCLUSION

Discovery and clinical application of new biomarkers, is expected to play a significant role in reshaping life science research and life science industry, thereby profoundly influencing the detection and treatment of many diseases. Biomarkers utilisation shows significant effect on patient health and economic status.

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