

ROLE OF BIOMARKERS IN MEDICAL SCIENCE

Abstract

Application of biomarkers in detection of different diseases is an emerging dynamic and powerful approach in medical science world-wide. Biomarker is a metric that reflects presence, level or severity of some disease state and in some cases reflects the prognosis of patient. As the term defines- biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention”. It provides an approach to understand disease epidemiology, randomized clinical trials, screening, diagnosis and prognosis measures. In this chapter we will focus on different types of cancer, cardiomyopathy, infectious, hepatic, psychiatric, genetic and autoimmunity disorders and biomarkers associated to them at different levels. This chapter will focus on the Classification of Biomarkers and their correlation with a wide repertoire of diseases along with their role in Precision medicine. The differential expression of biomarkers at particular stages is mentioned in detail for the better understanding of disease pattern for disease detection and diagnosis.

Keywords: It provides an approach to understand disease epidemiology, randomized clinical trials, screening, diagnosis and prognosis measures.

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I. INTRODUCTION

In medical diagnostics Biomarker is a metric that reflects severity, extent or presence of some disease state and in some cases reflects the prognosis of patient(Lim et.al., 2015). In 2001, a working group of the National Institutes of Health (NIH) coined the term biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” (Strimbu and Tavel, 2010). It provides a dynamic, powerful and accurate approach to understand a wide spectrum of disease epidemiology, screening, randomized clinical trials, diagnosis and prognosis. From the earliest manifestations to the extreme stages Biomarkers can reflect the entire spectrum of disease accurately and elaborately depicting all the intermediate stages (Mayeux, 2004). Throughout Generation a varied array of Biomarkers are used by epidemiologists, scientists, diagnostic experts and physicians to study human disease. The application of biomarkers in the diagnosis and management of cardiovascular disease, immunological disorders, infections and genetic disorders, Cancers, Neurological and Neuropsychiatric disorders and Autoimmune disorders are well known (Perera and Weinstein, 2000; Dunckley et.al., 2005; Gutierrez et.al., 2020; Prince, 2005). To explain briefly biomarkers can be regarded as characteristic biological properties which can be found and measured in parts of the body such as blood or tissue or they can be an external agent that is introduced into an organism to examine a particular organ function or other aspects of health. A common example is presence of antibodies indicates a particular infection and the level of Biomarker especially those detected in the body fluids gives an indication about progression and path physiology of the disease. These biomarkers can be Molecules, Gene products, hormones, Organic metabolites, complex organ functions or Cytoskeleton changes and sometimes a combination of two or more such factors (Lim et.al., 2015). Diagnosis and treatment of diseases (especially multifactor related complex diseases) in molecular level is driven by a biomarker based approach. Past decade showed a rapid discovery of Biomarkers driven by therapeutic modalities such Precision and Regenerative medicine guided by various branches of “Omics” along with computational technology such as AI (Artificial intelligence), machine learning and Deep learning(Bravo et.al., 2020). The selection of discriminating features related to any disease/ abnormal state via a biomarker is known as feature selection in machine learning languages. Applications of this latest technique are very uniquely designed to maintain the performance in a high throughput level. The discovery of biomarkers with application of such advance technology not only gives a accuracy measure for detection purpose but also the process has also become very fast(compared to conventional detection methods). It can be said that biomarkers will be the most widely applied upcoming detection procedure for medical assessment and will be preferred by clinicians and technicians. With fluctuations in expression biomarkers prominently and distinctively distinguishes between healthy state and compromised state of a biological system. The stages of any disease from primary to advance state and the extent of its expression are an important data to collect before providing any treatment.

This chapter will focus on the Classification of Biomarkers and their correlation with a wide repertoire of diseases along with their role in Precision medicine. The chapter also will deeply provide an insight to the types of biomarkers related to broadly classified diseases as well including cancer, cardiomyopathy, neurodegenerative, neuropsychiatric, infectious, hepatic, genetic and autoimmunity diseases.

II. CANCER BIOMARKERS

Biomarkers for cancer are measurable indicator of risk, prognosis and diagnosis of Cancers. The indicators include a variety of biomolecules such as Nucleic acid, proteins which are isolated from clinical samples such as blood (serum and plasma),saliva, swabs, tissue biopsy and CSF. On the other hand, genetic testing is conventionally different from cancer biomarker testing. This technique is used for detecting germline genetic variations which can be associated with hereditary cancer and/or cancer-associated syndrome(Sarhadi and Armengol 2022).

1. Brain and Nervous system Cancers: According to the data published by American Cancer society (<https://www.cancer.org/cancer/types.html>) chance factor of a person to develop a malignant tumor of Central Nervous System (CNS) i.e. the brain or spinal cord in their lifetime is less than 1% and is more prevalent in males than in females . There are various types of Brain and Nervous system cancers this includes - 1) Gliomas 2) Meningiomas 3)Schwanomas 4)Pituitary tumors 5)Pineal gland tumors 6) Primary Central Nervous system (CNS) Lymphoma 7)Medulloblastomas 8)Craniopharyngeomas 9)Choroid Plexus tumor. In India The five most frequent brain and Nervous system tumors were MB (11.4%),ependymal tumors (4.8%), craniopharyngioma (9.7%), astrocytoma (47.3%) and nerve sheath tumors (4.1%)¹⁰ whereas in USA and Europe the epidemiology shifts where gliomas take upto 78% of Brain and Central Nervous system tumors(<https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Brain-Tumors->:~:text=Gliomas%20are%20the%20most%20prevalent,oligodendroglial%20cells%20(or%20oligos). and 86.0% astrocytic (24% low grade, 63% high grade and 13% glioma NOS), 3.6% ependymal (85% low grade), 4.1% Embryonal tumours, 6.4% oligodendroglial (74% low grade) and (0.1%) choroid plexus carcinoma(Crocetti et.al. 2012). Though imaging studies Through CT scans and MRI are the routine screenings done by health professionals to ascertain the categorization and prognosis of brain tumors but several circulatory biomarkers have emerged in the recent findings which can detect different forms of Brain and central nervous system tumors some of which have been discussed in the Table 1.(A) below

Types of Cancer	Diagnostic Biomarkers	Prognostic Biomarkers	Predictive Biomarkers	Reference
Brain and Nervous system Cancers: Meningioma	Caspase-3(+), CD69(+) Prolactin(+), EGF(+), CCL24(+), Amphiregulin (+), HB-EGF(+),VEGFD (-) ,TGF- α (-),E-selectin (-), BAFF (-), IL-12(-),CCL9(-)Mutations in genes such as NF2 ,TRAF7(in Non-NF2 Tumors),KLF4,ATK1,SMO CHEK1,CLH22,SMARCE1 SMARCB, BAP1,CHEK2 , CHL22,PLOR2A	SERPINA1(+), CP(+), HPX (+), APOA1(+), ALB(+), C3(+), A1BG(+), HP(+) and APCS(+),	Mutations in gene such as NF2 , PD-L1, AKT1 mutation, PIK3CA mutation, VEGF,PDF,EGF	(Erkan et.al. 2019),(Roesler, Souza, and Isolan 2021),(Abbritti et.al. 2016),(Pawloski et.al. 2021)
Astrocytoma	GFAP δ (+), GFAP κ , RNU6(+), MiR-320, MiR-574-3p,KPAN2	KPNA2	Mutations in Gene BRAF- KIAA1549,BRAFV600E,IDH1,IDH2,TP53, ATRX,H3F3A,K27M, H3F3A G34R/V,EGFR,FGFR 2,PDGFRA,NF1,CDK N2A,PTEN	(Bodegraven et. al., 2019), (Manterola et.al., 2014), (Gousias et.al., 2012),(Sarhadi and Armengol 2022)
Craniopharyngioma	MMP-2,MMP-9, TrkA , β -catenin, Cyclin D1	MMPS, AnxA2(+),Cyclin D1(+), Ki-67(+).CXCL12(+) and CXCR4(+)	Mutationin BRAF V600E,Down regulation in APC, ITGA, MCAM, and TIMP4 andup regulation in CST7,	(Smith et.al., 2007; Y. Wang et.al., 2017),(C. Xu et.al., 2022),(Gong et.al., 2014)

			CTSK, CTSL1, CXCL12, CXCR4, FN1, FXYD5, ITGB3, MMP2, MMP3, MMP7, MMP9, NR4A3, PLAUR, TIMP2, and VEGFA	
Ependyoma	H3K27me3, ZFTA-RELA fusion status, Ki-67 high labeling index and L1CAM positivity	CDKN2A/2B loss ,chr1q loss and chr1q25 gain	C11orf95–RELA fusion protein ,YAP1 gene fusions, NF2 mutation,11q aberrations and 22q deletion	(Chapman et.al., 2023),(K. Y. Lim et.al., 2022),(Bonnin 2019)
GBM	EGFR mutation/ amplification ,MGMT promoter methylation IDH1/IDH2 mutation,circSMARC5(dysregulation)	MGMT(+),EGFR(+),PDGFR A(+),IDH(+),LOH10q,TP53(+),CTC(+),circHIPK3	miR-21(+),miR-10b(+), miR-15b(+),miR-137(-), miR-18d(-)	(Sasmita, Wong, and Ling, n.d.) , (Szopa et.al., n.d.)
Oligodendroglioma	9pLOH and/or deletion of the CDKN2A gene,PIK3CA mutations,	1p/19q codeletion with IDH mutation(better prognosis),TERT mutation with 1p/19q codeletion (+ve prognosis),CIC+IDH mutation (+ve prognosis),Polysomy of 1p19q(-ve prognosis),TERT mutations with 1p/19q	MGMT promoter methylation	(Wesseling, Van Den Bent, and Perry 2015)

		codeletion (+ve prognosis), TERT mutation without 1p/19q codeletion (-ve prognosis)		
Pituitary Neuroendocrine Tumors	H19, miR-143-5p, miR-423-5p, miR-21-5p, GNAS, USP8, USP48, HHIPL1, NNAT, RHOA, C5orf66 and RASSF	phosphorylation of serine 522 residue in correlates both with recurrence and invasion of NF-PitNETs, sst5TMD4 acts as a positive prognostic factor	SSTR2A, p-AKT (Ser743) or p-S6 (Ser240/244) expression levels, MAPK, RKIP, Low β -arrestin mRNA expression, ZAC1 upregulation	(Gossing, Frohme, and Radke 2020), (Barriuso et al., 2018), (Rai et al., 2022)
Vestibular schwannoma	VEGF(+), bFGF(+), ErbB family proteins(+), CPI-17- MYPT(+), NF- κ B, COX-2(+), High NLR, miR-29abc(+), miR-19(+), miR-340-5p(+), miR-21(+), miR-744(-), let-7b(-), MMP-2 and MMP-9, ADAM9(+), proteins like ABCA3, SCG1, KLF11, CA2D1, BASP1 and PRDX2	MMP-14(+) indicates poor prognosis, ki-67(+) increased recurrence of Vestibular schwannoma	VEGF(-), PDGFR(-)	(Zhang et al., 2021), (Ren et al., 2020).

Chordoma	Brachyury,SOX-9, CD24, Podoplanin, AE1/AE3	PD-L1(+),survivin(+),CDKN2A(mutation), CDK-12,inactivation of SMARCB1,D-dimer (+) and RDW (+)	PD-L1,CDK2NA(mutation),	(Rubino et al. 2022),(Barresiet.al., 2014),(Oakley, Fuhrer, and Seethala 2008)
Primitive neuroectodermal tumor	CD99, translocations involving the EWSR1 gene which is fused to an E26 transformation-specific (ETS) family gene (FLI-1, ERG, or ETS variant 1 (ETV1),	EWSR1 translocation, CDKN2A(deletions) TP53,	CD99, EWS-FLI1 fusion gene, IGF-1R, PARP1	(Louati et.al., 2018),(Shukla 2013)
Germinoma	HESRG, OCT4,PLAP, c-kit/CD117, NANOG, TFAP2c	miR-302/367, c-KIT /CD117, TP53,p53(+),ki67 (high proliferation index)	c-kit/CD117, miR-371a-373p, TP53-MDM2 signaling pathway,	(Hattab et.al., 2005),(Woo et.al., 2017), (Takami and Ichimura 2022; Ostertag et.al., 1987).
Hemangioblastoma	VEGF(+),VHL gene mutation on chromosome 3,	VHL mutations	VEGF*,VHL mutations *	(Sundblom et.al., 2022),(Gossage and Eisen 2010)

Pineoblastoma	MYCN(+),somatic mutation in DICER1	OLIG2(+),somatic mutation in ARID1A, KDM5C	MYC amplification,TRK fusion (role still unclear)	(Z. Xu et.al., 2022).(Kees et.al., 1998; Pratt, Sahm, and Aldape 2021),(Raleigh et.al., 2017;Laetsch et.al., 2018)
Medulloblastoma	miR-449a(-),OTX-2, amplification Myc-	WNT, SHH, Mutation on TP53 gene	WNT,SHH,Mutation on TP53 gene, chromosome 7 gain, chromosome 8 loss, and chromosome 11 loss	(Y. Li et.al., 2016), (Lu et.al., n.d.),(Goschzik et.al., 2018)
Glioma	TP53, PTEN, CDKN2A, EGFR(+),IDH1, IDH2 mutation,	IDH1, IDH2 mutation,p53Mutation.1p/19q codeletion, PTEN deletion, ATRX mutation	IDH1,IDH2 mutation, BRAF (V600E) mutations,EGFRvIII, MGMT promoter methylation	(H. Yan et.al., 2009),(Schindler et.al., 2011),(Jiao et.al., 2012; Montano et.al., 2011)

2. Cancers of Respiratory Tract: Cancers of respiratory tract mainly includes cancers of lungs, larynx (2.76 cases per 100,000 people per year) Nasopharyngeal cancer (2.12 per 100,000 people per year) and other less common cancers such as tracheal cancer (0.1 per 100,000 people per year) (Nocini et.al., 2020; Hao Yu et.al., 2022; Arul V. Chandran³, n.d.). Lung cancer remains one of the most deadliest and diagnosed cancers worldwide accounting 11.4% of all the cancer cases worldwide though it has been surpassed by Breast cancer in the recent years (Sung et.al., 2021). Detection of respiratory cancers particularly lung cancers involve a wide range of techniques which includes Imaging Techniques (Chest X-Ray, PET scan, CT-scan), biopsy, Genomic and proteomic analysis as well as Biomarker detection some of which have been discussed in the Table .1(B) below:

Types of Cancer	Diagnostic Biomarkers	Prognostic Biomarkers	Predictive Biomarkers	Reference
Cancers of Respiratory Tract: Lung cancer	ccCK18(+) and total CK18(+), Cyfra 21.1, EGFR9 (mutation), ALK rearrangement, p40, CD56, chromogranin, synaptophysin, KRAS (mutation) with TP-53 (co-mutation), BRAF mutation, EGFR mutation and amplification, miR-21, miR-214, miR-205, miR-92, miR-106, and miR-10a	CK18, ROS1 fusions, BRAF mutations, MET amplifications, KRAS (mutation) with TP-53 (co-mutation), miR-21, miR-155	EGFR9 (mutation), ALK rearrangement, KRAS (mutation) with TP-53 (co-mutation), EGFR mutation and amplification	(De Petris et.al., 2011), (Affandi et.al., 2018), (Kriegsman et.al., 2021), (Adderley, Blackhall, and Lindsay 2019; N. Yan et.al., 2022), (Bethune et.al., 2010), (Chalela et.al., 2017), (Xue et.al., 2016)
Laryngeal cancer	p53 (+), CD1(+), Ki-67 (high index value)	VEGF(+), CD31(+), CD1(+), Ki-67 (high index value), bcl-2(-) bcl-X _L (-), bax(+)	CD1(+), TP53 (mutation), bcl-2(-) bcl-X _L (-), HIF-1 α C1772T polymorphism, ERCC1(-)	(Schlüter et.al., 2018), (Cercelaru and Stepan 2017), (Zand et.al., 2020), (Mittal and Bansal 2020; Nix et.al., 2005), (Folic et.al., 2022; Y. Hasegawa et al. 2017)
Nasopharyngeal carcinoma	EBNA1, LMP1, LMP 2, EBV VCA-IgA and EA-IgA, CK18(+), lncRNA H19(+), MIR3936HG(+)	MiR-29c-3p(-), Bmi-1,	plasma load of Epstein-Barr viral (EBV) DNA, PD-L1	(Su et al. 2023; X.-M. Li et.al. 2009), (S. Wang, Claret, and Wu 2019), (Song et.al., 2006; Hsu et.al., 2017)

Tracheal carcinoma: No such molecular diagnostic, prognostic and predictive biomarkers are available for tracheal carcinoma. Diagnosis is mainly based on clinical symptoms and examination along with bronchoscopy and imaging techniques.

3. Gastro-intestinal Carcinoma: Gastrointestinal carcinoma encompasses a wide range of malignancies that affect various parts of digestive system which includes Colorectal cancers(10.2%) , Gastric carcinoma (5.7%), Liver cancers(4.7%), Esophageal cancers(3.2%) , pancreatic cancer(2.5%) and relatively rare group includes GIST(Gastrointestinal stromal tumors), Biliary tract cancer and Neuroendocrine tumors(Arnold et al. 2020).Though imaging techniques along with physical examination forms a major part of diagnosis many potential biomarkers have been studied for GI tract carcinomas some of which has been discussed below in the table 1C:

Type of cancer	Diagnostic Biomarker	Prognostic Biomarker	Predictive Biomarker	References
Gastro Intestinal cancers Colorectal Cancer	CEA,IL-10 (+),IL-17A(+),TGF-β(+),TNF-α(+)	CEA,BRAF (mutation),KRAS, TP53, 18q alteration	BRAF (mutation),KRAS(mutation),NRAS(mutation),BRAFV600 mutation,HER2 (+)	(Ma et al. 2022),(Nakayama, Hirota, and Shinozaki 2020),(Pino and Chung 2010; Custodio and Feliu 2013),(Ivanova et al. 2022)
Gastric Cancer	CA72-4,GKN1(-), TFF3(+),Helicobacter pylori Antibodies(+)	miR-21,miR-145,miR-184, miR-20b, miR-9-1, miR-9-2, miR-1537, miR-549,miR-802, HER2,Ki-67,VEGF,E-cadherin	Ki-67,HER2(+), MET amplification, MET(+),VEGF-A,Low mRNA expression of EGFR/FGFR2/MYC	(M. Li et al. 2020),(Yoon et al. 2019),(Yuan, Wang, and Zhang 2018),(Ko et al. 2017),(Xiong et al. 2019),(D.-H. Liu 2001),(Kim and Green 2014)
Liver cancer	AFP(+),AFP-L3%(+),DCP(+),GPC3(+), OPN(+)	GPC3,AFP,AFP-L3% CTNNB1	PDGFR, VEGF-R, KIT, FGFR1,FGF19/FGFR4,PD-L1	(F. Zhou et al. 2018),(De et al. 2016),(Abdel-Hafiz et al. 2018),(L. Chen et al. 2021),(Gao et al. 2017),(Brunetti et al. 2019),(X. Zhou et al. 2023)

Esophageal carcinoma	p53 antibody CEA,SCC,C YFRA211,C DC25B- Antibodies, miR-129	CYFRA 21-1 ,SCC-Ag,NSE,HER2	BRCA1/2 (mutation),HER(amplification)	(Yin and Liu 2020),(Ju et al. 2022),(Iqbal and Iqbal 2014), (Tan et al. 2016),(Zimmer et al. 2021),(Plum et al. 2019)
Pancreatic carcinoma	CA19-9(+),VEGF,F GF-10/KGF-2,Tgf- β ,CA125.Ost eonectin(+),L aminin γ 2(+),Soluble CD40 ligand,C4b- binding protein a- chain, REG1 β .SYC N(+),GPNM B,MMP-7,MMP-12	Laminin γ 2,UL16 binding protein 2,Soluble CD40 ligand,VEGF-A,ICAM-1	CXCL11.CEA CAM1,BRCA1/2(mutation),KRAS(mutation)PD-L1,	(O'Neill and Stoita 2021),(Amaral et al. 2023),(Hu et al. 2019)
GIST	DOG1, Ki-67, SDH(-),PKC theta,PDGFR A	Ki-67,KIT(mutation),CDH1(methylation),SETD2,SLIT and NTRK,ROR2	SDH(promoter hypermethylation),BRAF(mutation at exon 15),PDGFRA (mutations), SDH, BRAFV600	(Sözütek et al. 2014),(De Silva et al. 2021),(Motegi et al. 2005),(X. Liu and Chu 2019),(Incorvaia et al. 2021),(Huss et al. 2017)
Biliary Tract cancer	CA19-9(+),CA125.(+),AFP(+),MUC1(+), IDH1 or IDH2 mutataion	CA19-9(+),CYFRA 21-1(+),MMP-7(+), suPAR,, AGR ratio, miR-150(+),NKG2D(+), CD55(+), CD97(+)	IDH1 or IDH2 mutataion,FGFR2(+),VEGFR2 ,HER2/neu(+)	(Chaube et al. 2006),(Tao et al. 2010),(S. Y. Park et al. 2009),(Sumbly, Landry, and Rizzo 2022),(Pavicevic et al. 2022)

4. Hematological Malignancies: A hematological malignancy includes a variety of diseases that arise from bone marrow. Malignancies encompass leukemia's, lymphomas, and multiple myeloma. Each of them has a unique pathophysiology, clinical presentation and therapeutic approaches. Molecular diagnostics has a wide application in the field of

Hematology and hematopathology which help in guiding diagnosis, sub-classification, prognosis and outcomes of therapeutic intervention.-Biomarkers involved in hematological malignancies include chromosomal translocations such as t(9;22) (BCR-ABL1) fusion in Leukemia and MYC, BCL2, and BCL6 Translocations in lymphomas. Few biomarkers are discussed below in the table 1.D

Type of Cancer	Diagnostic	Prognostic	Predictive	Reference
Hematological Malignancies: Leukemia	t(8;21)(AML), t(15;17)(AML), inversion 16(AML),trisomy8 (AML), BCR-ABL fusion protein (CML))	Mutation in CEBPA,DNMT3 A, IDH1/2, TET2(AML),W T1(AML),ERG expression(AML) BAALC(AML) expression,FLT3 -ITD Mutation(AML) NOB1(CML),D DX47(CML), IGSF2(CML), LTB4R(CML), SCARB1(CML), and SLC25A3(CM)	FLT3(AML), NPM(AML), CEBP(AML), SAMHD1(AML), HMGCLL1(CM) , BCR-ABL kinase	(Hussaini 2015; Kiyoi, Kawashima, and Ishikawa 2020),(Schneider et al. 2017),(Prada- Arismendy, Arroyave, and Röthlisberger 2017),(J.-H. Park et al. 2019)
Lymphoma	BCL6,Myc(Burkitt lymphoma), MYD88 ^{L265P} (mutation), CIITA translocation(HL), ID3 and MYC, TP ST2 and RE mutati on (BL), CD30(HL), Bcl- 6(TCL), SOX- 11 (MCL),	BCL6(+),TP53 mutation(BCL), MYD88(L- BCL), Bcl- 6(TCL), p53	TP53 mutation(BCL), MYC-IG translocation,L MO2(BCL), BCL6(BCL), FN1(BCL), CCND2(BCL), SCYA39(BCL),	(Sun, Medeiros, and Young 2016)
Multiple Myeloma	t(11;14), t(4;14), t(14;16), t(6;14),t(14;20), trisomies, and del(17p),M protein, VEGF(+),HGF(+), angiopoietins(+) and JunB(+),miR- 15a(-)miR-16a(-)miR-17(+),miR- 19b(-),miR-25(-)	M protein level, β2- microglobulin levels,FGF-2,	VEGF(+),HGF(+) ,angiopoietins(+) and JunB(+)(HIF)- 2α(+)	(Soliman, Das, and Teoh 2021; Rajkumar 2020)

5. Gynecologic Malignancies: Most common malignancies of the female reproductive system include Ovarian, endometrial, and cervical cancers. The most common gynecologic cancers affecting women worldwide are Ovarian and cervical cancers. Although Cervical cancer is declining in number and trend, but still remains the second most common cancer in women after breast cancer, which is till now the most deadly and frequent cancer worldwide (<https://www.who.int/news-room/fact-sheets/detail/cancer>). In India every single year, 122,844 women are diagnosed on an average with cervical cancer and 67,477 die for the same (Maheshwari, Kumar, and Mahantshetty 2016). Intermediate in frequency between cervical cancer and endometrial cancers, but till now reported as the most fatal, is ovarian cancer which killed about 15000 women out of 20000 diagnosed in US (Ueda et al. 2010). Hence, in case of endometrial, ovarian and cervical cancers, it is difficult to detect the disease at preliminary stage. In this section (Table 1.E) we discuss about few of the biomarkers which are already in use along with few novel Biomarkers for future which helps in better detection, prognosis and management of gynecologic cancers, including endometrial, ovarian and cervical cancers.

Type of cancer	Diagnostic Biomarker	Prognostic Biomarker	Predictive Biomarker	Reference
Gynecologic Malignancies: Ovarian Cancer	CA 125(+), CA 19-9(+), HE4(+), ApoA-1(+), IGFII, MIF, BRCA1 and BRCA2, PTEN, CDH1	CA125, KLKs, OPN, ALDH1	VEGF, Mesothelin, lncRNA and mRNA, GSTP, FOLR1, BRCA1 and BRCA2	(Ueda et al. 2010; Atallah et al. 2021)
Endometrial Cancer	CA125(+), HE4(+), ApoA-1(+), CA 72-4(+), CEA(+), MLH1, MSH2, MSH6, PMS2, and EPCAM.	CA 15-3, E3, E1-S, NLR, MLR, PLR, SII etc	EGFR tyrosine kinases, PTEN, PI3K, Bcl-2, p53	(Ueda et al. 2010), (Njoku, Barr, and Crosbie 2022; Banno et al. 2012)
Cervical Cancer	SCC(+), CYFRA 21-1(+), CA 125(+), CA 19-9(+), IAP(+), CEA(+), YKL-40(+)	CYFRA 21-1, IAP, CAIX, GLUT 1	GLUT1, CAIX, HKI	(Ueda et al. 2010; Moreno-Acosta et al. 2016)

Breast Cancer	TFF1, TFF2, TFF3, CEA, CA 15–3, miR-21, miR-1246, miR-155, miR-29a, miR-146a, miR-373, miR589, miR-221/222 cluster, miR-9, miR10b, miR-96, miR-181, miR-375, and miR-520c, HER2, Ki67, BRCA1 and BRCA2, PTEN, CDH1	CA 15–3, miR-155, c-erbB-2, TGF- α , EGFr, bcl-2	, miR-1246, miR-155, miR-29a, miR-146a, miR-373, miR589, miR-221/222 cluster, miR-9, miR10b, miR-96, miR-181, miR-375, and miR-520c, miR-7, Axis of RNA/miR-7-5p/Raf1, TRAF4, Er α 36, HER2, Ki67, BRCA1 and BRCA2	(Afzal et al. 2022; Beenken et al. 2001)
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We have grouped breast cancer as a part of gynecologic cancer as they come under the umbrella of "women's cancers" due to their predominant occurrence in females and also to highlight the importance of breast cancer and the novel a wide range of biomarkers associated with it however they are generally classified differently based on the anatomical origin and their clinical management

III. CARDIOMYOPATHY BIOMARKERS

Cardiomyopathy is disease of heart muscle which makes the heart work harder to pump blood to the rest of body. Cardiomyopathy can lead to heart failure. The type of cardiomyopathies include 1) Hypertrophic cardiomyopathy (1:250/500) 2) Dilated Cardiomyopathy (1:250/500) 3) Arrhythmogenic cardiomyopathy (1:250/5000) 4) Restrictive Cardiomyopathy (uncommon) (McKenna, Maron, and Thiene 2017).

1. Hypertrophic Cardiomyopathy: Hypertrophic cardiomyopathy (HCM) is a hereditary condition distinguished by the thickening of the left ventricular wall, unexplained by other hemodynamic stress factors. At a microscopic level, it showcases a pattern of disordered heart muscle cells, fibrosis, and irregularities in the tiny blood vessels within the heart muscle. HCM is singular in nature, being a monogenic heart ailment, and is typically inherited in an autosomal dominant manner with varying degrees of expression. In the broader population, its prevalence stands at about 1 in every 500 individuals (Cambroner et al. 2008). The most promising field where biomarkers have played essential role in cardiomyopathies are ischaemic heart disease and heart failure. Various biomarkers have shed light on the pathophysiology of atheromatous plaque, as explored in Cambroner et al. 2008. Specific biomarkers like B-type Natriuretic Peptide and N-terminal pro b-type Natriuretic Peptide are of interest because their levels elevate in reaction to stress on the myocardial wall. Additionally, high-sensitivity Troponins, as well as indicators of myocardial fibrosis such as Galectin-3 (Gal-3), play crucial roles.

Moreover, markers reflecting collagen turnover, like PICP (C-terminal propeptide of procollagen type I) and PIIINP (N-terminal propeptide of procollagen type III), are also pivotal in understanding cardiac pathologies. Elevated levels of which reflect the increased collagen turnover seen in the myocardial fibrosis of HCM.

- 2. Dilated Cardiomyopathy:** Dilated cardiomyopathy (DCM) is a cardiac muscle disorder characterized by ventricular chamber enlargement and systolic dysfunction with normal ventricular wall thickness. The etiologies of DCM are diverse and ranges from genetic mutations to post viral response. Though a considerable amount of progress has been made in recent years DCM continues to be an important reason behind cardiac transplant. Several biomarkers for example C-reactive protein (CRP), Galectin 3(Gal-3), B-Type Natriuretic Peptide (BNP) and N-Terminal-pro Hormone BNP (NT-proBNP) have emerged which proved to be of great deal of importance in diagnostic, prognostic and management utility in DCM(Anghel et al. 2021).
- 3. Arrhythmogenic Cardiomyopathy:** Arrhythmogenic cardiomyopathy (AC), also referred to as arrhythmogenic right ventricular dysplasia, is a comparatively rare genetic disorder of the heart muscle. This condition is marked by fibrofatty substitutions in the myocardium and is linked with ventricular arrhythmias. While AC predominantly impacts the heart's right ventricle, it can also manifest in the left ventricle. Biventricular involvement in AC may progress to heart failure, as noted by Akdis et al. 2022. Recent breakthroughs in genetic testing have pinpointed non-desmosomal gene mutations, which are often linked to biventricular (BiV) and left ventricular (LV) dominant forms of ARVC, as stated in Akdis et al. 2022. Established diagnostic and prognostic biomarkers for this condition include the Brain-derived natriuretic peptide (BNP) and its N-terminal variant (NT-pro BNP). Recently, newer biomarkers have been identified, such as the soluble suppression of tumorigenicity-2 (sST2), galectin-3 (Gal-3), and growth differentiation factor-15 (GDF-15).
- 4. Restrictive Cardiomyopathy :** Restrictive cardiomyopathy (RCM) is a cardiac muscle disorder which is characterized by dystolic dysfunction of non-dilated Ventricle .The major reasons behind Restrictive Cardiomyopathy are Cardiac amyloidoisis,cardiac sarcodiasis and cardiac hemachromatosis. ECG (Electro cardiogram)is one of the first tools used in diagnosis along with CMR (Cardiac magnetic resonance).Certain biomarkers have emerged as important diagnostic and prognostic tool such as troponin T, B-type natriuretic peptide (BNP), and pro-BNP(Rene R. Diaz4. and Kristen N. Brown1, n.d.)

Types of Cardiomyopathies	Diagnostic Biomarker	Prognostic Biomarker	Predictive Biomarker	Reference
Hypertrophic cardiomyopathy	IL-6(+), TNF- α (+), ANP(+), BNP(+), s-Fas(+), sTNFR I(+), CRP(+), Endothelin-1(+), PICP(+),	MYBPC3 variants, MMP, TIMP, Gal-3, Cardiotrophin	BNP and NT-proBNP LYVE1(-), MAFB(-), and MT1M(-)	(Zen et al. 2005), (Penicka et al. 2001), (Dimitrow et al. 2008), (Fassbach and Schwartzkopff 2005), (K. Hasegawa et al. 1996, 1), (Masson 2006; Jansen et al. 2021; Matthia et al. 2022)
Dilated Cardiomyopathy	CRP(+), NLR ratio, Gal-3(+), Chemerin(+), TNF- α , BNP(+), N-Terminal-pro Hormone BNP(+), ST2(+), H-FABP(+), sMMP-1, MMP-9, T-cadherin(+)	CRP(+), IL-6(+), (TNF)- α (+), ST2(+), Syndecan-1(+), GDF-15(+), Syndecan-4	BNP and NT-proBNP, MD-2	(Anghel et al. 2021; Masson 2006; Riad et al. 2018)
Arrhythmogenic cardiomyopathy	NT-pro BNP(+), BNP(+), BIN1(+)	sST2(+), I-3(+), and GDF-15(+), BIN1(+), connexin-43, miR-130a(+)	BNP and NT-proBNP	(Akdis et al. 2022; Masson 2006; Alcalde et al. 2023)
Restrictive Cardiomyopathy	NP(+), BNP(+), NT-pro BNP(+), TNN T2 TNNI3.	Galectin-3(Gal 3), TNNT2, TNNI3	BNP and NT-proBNP, amyloid load,	Andrew Connelly, n.d.), (Hara et al. 2020), (Masson 2006)

IV. AUTOIMMUNITY BIOMARKERS

A diverse range of autoimmune and rheumatic diseases exist, wherein the immune system erroneously attacks the body's own tissues. These disorders target different organs and systems, such as Multiple sclerosis (MS): Primarily affects the brain, Rheumatoid arthritis (RA): Predominantly targets the joints, Type 1 diabetes (T1D): Primarily involves the pancreas, Sjogren's syndrome (SS): Chiefly affects the salivary glands, Celiac disease: Predominantly impacts the small intestine, Systemic lupus erythematosus (SLE): Can affect nearly every organ and system within the body.

Each of these conditions demonstrates how the immune system, instead of protecting the body, can sometimes turn against it, leading to a myriad of symptoms and complications (Fenton and Pedersen 2023; Singh et al. 2019). Production of autoantibodies, activation of immune cells, increased expression of pro-inflammatory cytokines, and activation of type I interferons are signature of Autoimmune disorders. Though improvements have been made in treatments and Diagnostic tools the time taken for the patients to be diagnosed is quite lengthy and the procedure it involves is too long to bare with the main treatment for these disease still relies on non-specific anti-inflammatory drugs. Biomarkers play a pivotal role in the diagnosis, prognosis, and prediction of therapeutic response in autoimmune diseases cutting short the long procedure involved previously. Biomarkers generally involve circulatory macromolecules in serum and also genetic variations linked with prediction of autoimmune disorders. Though there are more than 80 types of autoimmune diseases (<https://medlineplus.gov/autoimmunedisorders.html#:~:text=There%20are%20more%20than%2080,Autoimmune%20hepatitis%20affects%20the%20liver.>) We will discuss about few notable autoimmune diseases and the biomarkers associated with it in the table 3A given below:

- 1. Multiple Sclerosis:** Multiple sclerosis (MS) is a long-term, immune-mediated disease characterized by inflammation and the loss of the protective myelin sheath around nerve fibers in the central nervous system (CNS). This disease typically manifests in individuals aged between 20 and 40 years. Relapsing-remitting multiple sclerosis (RRMS), the most prevalent subtype of MS, is marked by episodes of symptom exacerbation followed by periods of recovery. Numerous treatment modalities currently exist to decrease the frequency of relapses and control neuroinflammation in RRMS patients but still it is crucial to find a specific and sensitive biomarker which will provide essential clinical readout based on both diagnosis and prognosis for example : Recent development of sensitive assays has identified Nfl (Neurofilament light chain) as potential biomarker but Nfl didnt emerge as the only biomarker in the assay as there's a notable similarity in the range of serum NfL (sNfL) levels in individuals with MS when compared to healthy controls. Consequently, both blood and cerebrospinal fluid (CSF) biomarkers indicating axonal injury, neuronal damage, glial dysfunction, demyelination, and inflammation have been thoroughly researched as potential actionable biomarkers for MS (Yang et al. 2022).
- 2. Rheumatoid Arthritis (RA):** Rheumatoid arthritis (RA) is a pervasive chronic inflammatory condition that, if left undiagnosed or improperly managed, can lead to joint deformities and functional limitations. Recognizing and treating RA promptly is essential for effective management, increasing the likelihood of remission, and averting lasting clinical and radiographic harm. In clinical settings, rheumatologists often employ a scoring system formulated by the American College of Rheumatology and the European

League Against Rheumatism (ACR/EULAR) to validate the diagnosis of Rheumatoid arthritis (Chaube et al. 2006). Few novel biomarkers are now being available for routine clinical use this includes rheumatoid factor, C-reactive protein and erythrocyte sedimentation rate for diagnosis and prognosis of Rheumatoid arthritis.

- 3. Type 1 Diabetes (T1D):** Type 1 diabetes (T1D) is a chronic autoimmune condition marked by a lack of insulin due to the autoimmune-mediated obliteration of insulin-producing pancreatic β -cells found in the islets of Langerhans. While lifelong insulin administration remains a standard approach for managing glucose levels in T1D patients, no definitive curative treatments are currently available for this ailment. Biomarkers play a pivotal role in the diagnosis, prognosis, and potential prediction of therapeutic responses or disease progression in T1D. While the development of specific blood serum (or plasma) biomarkers holds considerable appeal, crafting such serum markers, especially those indicating pancreatic β -cell death or stress, has proven to be a formidable challenge in the context of T1D. Until now the biomarkers implemented mainly include glucose, HbA_{1c}, c-peptide, and autoantibodies (AAb) for clinical practice (Yi, Swensen, and Qian 2018).
- 4. Sjogren's Syndrome:** Sjögren's syndrome is a persistent systemic inflammatory autoimmune condition marked by keratoconjunctivitis and xerostomia. Beyond the primary glandular symptoms, the disease's manifestations extend to include synovitis, interstitial lung disease, neuropathy, renal disease, vasculitis, and autoimmune cytopenias. Alarming, patients diagnosed with Sjögren's syndrome exhibit a 6.5-fold elevated risk of developing non-Hodgkin's lymphoma, a risk surge that surpasses that associated with any other autoimmune ailment (W. Chen et al. 2015). The disease can be primary (without any associated autoimmune disease) or secondary (in association with another autoimmune disease, such as rheumatoid arthritis or systemic lupus). Diagnosis mainly occurs through labial salivary gland biopsy and is often helpful to diagnose the pSS disease according to revised 2002 American-European criteria (W. Chen et al. 2015). As biopsy involves an invasive procedure hence noninvasive biomarkers are needed for the diagnosis and prognosis of Sjogren' syndrome which includes Carbonic Anhydrase-1 (CA-I) and cytokines such as IL-4 and IL-5.
- 5. Celiac Disease:** Celiac disease is a systemic autoimmune condition triggered by the consumption of gluten, a protein present in wheat, barley, and rye, resulting in damage to the small intestine. Previously perceived as a rarity, celiac disease has emerged as one of the more prevalent conditions worldwide. The primary therapeutic approach involves abstaining from gluten or maintaining a gluten-free diet. Currently, there isn't a definitive gold standard test for its diagnosis. Instead, identification largely relies on presenting physical symptoms, detection of a celiac-specific antibody (like anti-tissue transglutaminase antibody, anti-endomysial antibody, or anti-deamidated gliadin peptide antibody), and the observation of villous abnormalities in the small intestine. Enteropathy is one of the significant hallmark complication of celiac disease which can only be investigated by endoscopic examination which is perceived as invasive hence this lead to development and identification of novel non invasive biomarkers which has a definite role in diagnosis of the disease such as Anti-gliadin antibody (AGA) Anti-endomysial antibody (AEA) (Singh et al. 2019).

6. Systemic Lupus Erythematosus : Systemic lupus erythematosus (SLE) is multisystemic autoimmune disease with a complicated etiology and is characterized by peculiar activity of the immune system.(Haitao Yu, Nagafuchi, and Fujio 2021) A wide range of Clinical symptoms are manifested by SLE including renal, dermatological, neuropsychiatric, and cardiovascular symptoms. A multidisciplinary approach should be manifested to treat SLE in terms of controlling the symptoms and delay the progression of the disease. Biomarkers, especially immunological biomarkers, have emerged to aid in better diagnosis of SLE and determine its pathophysiological processes. For example- Antinuclear Antibodies (ANA) and urinary markers like MCP-1(Monocyte Chemoattractant Protein-1), and TWEAK (Tumor Necrosis Factor-like Weak Inducer of Apoptosis) can provide information on renal disease status and prognosis.

Type of Autoimmune Diseases	Diagnostic Biomarker	Prognostic Biomarker	Predictive biomarker	Reference
Multiple sclerosis	cNfL(+), SNfI(+), APP(+),TUBβ(+),NSE(-),AQP4(-),MOG(+)	cNfL(+), tau (+), GFAP, S100β(+)	cNfL(+),CHI3 L1(+), HSP70(+), HSP90(+)	(Yang et.al., 2022)
Rheumatoid arthritis	RF(+),anti-CCP2(+),anti-MCV,serum-14-3-3eta,anti-CarP,	DAS28-CRP, SDAI, DAS28-ESR, IL-6, serum VEGF, serum COMP,CTX-I, CTX-II, MMP-1 and MMP-3	anti-CCP2(+)	(Shapiro 2021)
Type 1 Diabetes	C-peptide(-), ICA,GADA,IA-2A, ZNT8A,ADIPOQ,APOA4,APOC4,AZGP1,BTD ,KNG1,LUM,SERPINA6	C-Peptide, HbA1c	ICA,GADA,IA-2A, ZNT8A	(Yi, Swensen, and Qian 2018)
Sjogren's syndrome	Flt-3L(+),IL-4(+),IL-5(+),clausterin,cathepsin, CA-I(-), BAFF(+), RF(+), ANA(+), Anti-SSA (Ro) and Anti-SSB (La) antibodies	Flt-3L(+), CXCL13,C4, Polymorphisms in TNFSF13B and TNFRSF13C	MxA(-),IFN type I a,	(Brito-Zerón et.al., 2016),(W. Chen et.al., 2015)
Celiac Disease	(AGA),(AEA),Anti-tissue transglutaminase	CYP3A4,Plasma citrulline, I-FABP, Reg 1α	HLA-DQ haplotyping	(Singh et.al., 2019)

	(tTG)- TG2, TG6, TG3 (DGP), Synthetic neo-epitopes tTG-DGP comple			
Systemic Lupus Erythematosus (SLE)	Serum ANA, C3(-), C4(-), ANA(+), ESR(+), CRP(-), anti-C1qAb, Chemokines (CXCL-16, TGF- β , TWEAK, MCP-1, V-CAM, ICAM)	Anti-dsDNA antibodies, Paraoxonase-1 and HDL, Serum anti-dsDNA Ab, serum Anti-Sm Ab, IL-10(+), IL-6(+), TNF- α (+), IFN- γ (+), MCP-1(+), IP-10(+)	Cardiac Troponin T	(Haitao Yu, Nagafuchi, and Fujio 2021)

V. BIOMARKERS IN INFECTIOUS DISEASES

Infectious diseases arise from the invasion of pathogenic microorganisms, including viruses, bacteria, parasites, and fungi. Globally, these diseases have exerted significant strain on health and economic infrastructures. In developing nations, notably India, research indicates that infectious diseases remain a persistent challenge, with over 33% of the country's afflicted population grappling with such ailments (Ram and Thakur 2022). Among the myriad infectious diseases prevalent globally, HIV, tuberculosis, and malaria stand out for their significant contribution to global mortality rates. Additionally, numerous neglected tropical diseases, including Chagas disease, dengue, yellow fever, West Nile, Japanese encephalitis, and chikungunya, are recognized as formidable threats on the global health landscape (Hwang, Hwang, and Bueno 2018); about half of the world population face direct threat of developing fatal illness due to infectious diseases and hence early detection of such infections is estimated to significantly reduce the mortality rate. Hence discovering highly sensitive and specific biomarkers for diagnosis and prognosis has really been a challenge as they can indicate the presence of an infection, the stage or severity of an infection, or the body's response to treatment. For example: Adenosine deaminase (ADA) has been a major diagnostic marker for Tuberculosis (TB) on the other hand procalcitonin (PCT) assay, is used that can discriminate between a viral and a bacterial infection and has been approved by Food and Drug Administration (FDA). Biomarkers for few infectious diseases have been enlisted below.

Types of Infectious Diseases	Diagnostic Biomarker	Prognostic Biomarker	Predictive Biomarker	Reference
Viral infections: Influenza	Influenza viral RNA CRP (+), PBI, MMP8, TCN1, RETN, OLFM4,	CRP, BPI, MMP8, TCN1, RETN, OLFM4,	IL-6, IL-10, and TNF- α	(Vasileva and Badawi 2019), (S. Liu et al., 2021), (Z. F. Wang et al., 2011), (To

	ELANE, LTF, LCN2, DEFA4 and HP	ELANE, LTF, LCN2, DEFA4 ,HP, D-dimer		et.al., 2010)
HIV	hs-CRP(+),IL-6(+),D-dimer(+),protein S(-), protein C(-),LPS(+),16s DNA,sCD14(+),IFN- γ (+),I-FABP, HLA-DR, CD38, Ki67, Caspase 3,sTNFR-1	PPI, p24	d-Dimer, IL-6,	(Rubio Caballero et.al., 1999; Nixon and Landay 2010)
Hepatitis	IgM anti-HBc, IgG anti-HBc, HBsAg, HBV DNA,	HBcrAg, M2BPGi	HBcrAg,	(Baudi, Inoue, and Tanaka 2020)
COVID-19:	CRP(+),ESR(+), IL-6 (+),NSE, LDH,AST, CK-MB, myoglobin, D-dimer,BNP(+),NT-proBNP(+)	NSE, LDH,AST,Surfactant protein-D, angiopoietin-2,CRP, ferritin,Myoglobin,low HDL	D-dimer.,IL6, CRP levels	(Battaglini et.al., 2022; Guaraldi et.al., 2020),(F. Liu et.al., 2020)
Bacterial Infection: Tuberculosis	Ag85A(+), Ag85B(+), and Ag85C(+),Mtb DNA,LAM, IFN γ ,IFN $\alpha\beta$, IP10(+),CD27(-),Ki-67, Mtb-specific CD4+ T-cell, Rv1733c, Rv2029c, Rv2628 and HBHA	plasma chitinase, IDO, Ag85A, interferon (IFN)- γ specific T-cells,	IP10(+), VEGF, HO-1, MMPs, IL11	(Kumar et.al., 2023; Goletti et.al., 2016; Petruccioli et.al., 2016)
Infection caused by protozoa: Malaria	PCT, var genes, CK-MB, CKD-EPI eGFR, pLDH, HMGB1,D-dimers,carboxyhemoglobin, pfhrp2	CRP, Ang-2, Ang-2/1 ratio, PfHRP2, VCAM-1, sICAM-1,TNF- α , vitronectin, IL-10, CXCL10,	pfhrp2	(Foko et.al., 2022; Atroosh et.al., 2022)

Dengue	NS1 antigen, IFN- γ , TNF- α , IL-1, IL-6, IL-8, IL-10, CCL2 (MCP-1) and CCL5 (RANTES), IFN- γ , TNF- α , IL-1 β , IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-15, IL-17, IL-18, MIF and chemokines CCL2, CCL4, CCL5, and CXCL10 (IP-10)	Ang-1(-), ngptl3(+), sKDR(+), sEng(+), sICAM-1(+), CRP(+), CXCL10/IP-10(+), CHI3L1(+), C5a(+), Factor D(+), CD95(+), IL-6(+), IL-10(+), IFN- γ (+), MIF(+), and CCL-4(+)	IL-6(+), IL-10(+), IFN- γ (+), MIF(+), and CCL-4(+)	(Alcon et.al., 2002), (John, Lin, and Perng 2015; Conroy et.al., 2015)
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1. Neurodegenerative Disease: Neurodegenerative diseases are caused by rapid and consistent loss of selectively vulnerable neuron population. The process is contradictory to static neuronal loss as the later may get initiated due to any metabolic disorder or toxicity effect within a system. The clinical classifications of neurodegenerative diseases are broadly categorized as extra-pyramidal and pyramidal movement disorders and behavioral or cognitive disorders as the most common ones. In general neurodegenerative diseases are marked by specific protein accumulation and much anatomic vulnerability. Different particular neurodegenerative disease may show different effects in very fundamental processes of a living organism leading to neuronal dysfunction and death. The particular pathways that may lead to such effects can be proteotoxic stress, abnormalities in ubiquitin- proteasomal reactions, autophagosomal and lysosomal system dysfunctions, PCD (Programmed Cell Death), oxidative stress and neuro-inflammation. The detection of neurodegenerative diseases are a matter of big concern as the process becomes critical since the evidence of particular protein factor accumulation is subjected under question as it will be checked only after the onset of symptoms in a particular organism and not in its healthy state (Gibb and Lees 1988; Sparks et al. 1994; Schmitt et al. 2000; Adler et al. 2010; Evidente et al. 2011; Frigerio et al. 2011; Milenkovic and Kovacs 2013; Dugger et al. 2014c). The other important factor making the disease diagnosis a difficult task is onset of more than one neurodegenerative diseases at the concurrent time in a particular individual (Uchikado et al. 2006a; Dugger et al. 2014a)

Most common types of neurodegenerative disorders are taupathies, TDP 43 (transactivation response DNA binding protein-43 proteinopathies, amyloidoses and α -synucleinopathies. The following chart represents the type of most common neurodegenerative disorders-

Type	Examples
Amyloidoses	Alzheimer's disease, Familial British dementia, Gerstmann-Sträussler-Scheinker disease etc.
TDP-43 proteinopathies	Progressive muscular atrophy, Amyotrophic lateral sclerosis, Frontotemporal lobar degeneration, Primary lateral sclerosis etc.
Taupathies	Chronic traumatic encephalopathy, Pick's disease, corticobasal degeneration etc.
Synucleopathies	Multiple system atrophy, Lewy body disorders etc.

(Reference: Dugger and Dickson, 2017)

All specific neuropathological diagnosis for neurodegenerative disorders are based on abnormal protein conformation and their accumulation. Some example of such protein accumulations are

Disease	Protein accumulated
Pick's disease	3R tau
Progressive supranuclear palsy, Argyrophilic grain disease, corticobasal degeneration	4R tau
Chronic traumatic encephalopathy, Primary age related taupathy,	3R+4R tau
Alzheimer's disease	A β , 3R+4R tau
Lewy body disorder, Multiple system atrophy	α – Synuclein
Primary lateral sclerosis, Frontotemporal lobar degeneration, Progressive muscular atrophy	TDP-43
Familial British dementia	ABRI
Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease	PrP

(Reference: Dugger and Dickson, 2017)

As the accumulation and conformational change of the aforesaid proteins are directly related to expression of neurodegenerative diseases, these are regarded as biological markers for the respective diseases.

- 2. Neuropsychiatry Disorders:** Some of the common Neuropsychiatric disorders are Palsies, Attention deficit disorders, Schizophrenia, Cognitive deficit disorder, Dementia etc. In these particular types of disorders both neurological and psychiatric sides are compromised in the effected individual. The effect of the disease affect both nervous system(brain especially), emotional sides and mood of a particular individual. A mechanistic interaction between nervous system and immune system of an individual leads to onset of such disorders. An exposure to different chemicals, mycotoxins, molds and other biological as well as environmental contaminations may lead to initiation of neuropsychiatric disorders (Empting, 2009). Classification of biological markers associated with neuropsychiatric diseases is elaborately described by Davis et.al., 2014. Davis and his team has characterized the biomarkers of neuropsychiatric diseases broadly in six groups-

- 1. Biomarkers of Risk:** This type of biomarkers gives a quantitative idea of how and with what factors a disease is forming in an individual and how vulnerable it can become. The different levels of such indicators provide the diagnostic expert to detect the type and extent of a neuropsychiatric disease and determine the risk factors associated with it. e.g.- In pregnant women Oestrogen-mediated epigenetic DNA methylation pattern leads to high risk of post-partum depression (Guintivano et.al., 2014).
- 2. Biomarkers of Diagnosis Or Trait:** Diagnostic biomarkers ensure the presence of certain neuropsychiatric disease. A good diagnostic biomarker will signify only one type of disorder. E.g.- Diagnostic biomarker for Alzheimer's disease is senile plaques and neurofibrillary tangles (Schwarz et.al.,2012).
- 3. Biomarkers of Acuity:** The severity of a particular disease is measurable with the presence of a biomarker at particular state. E.g.- expression of IL-6, IL-10, neurotrophin-3, protein carbonyl etc. are associated with acute episodes of mania in bipolar disorder(Kapczinski et.al., 2010).
- 4. Biomarkers of Stage:** Categorization of exact stage of illness is assured by the biomarkers of stage. In neuropsychiatric disorder analysis detection of particular stage is very crucial. E.g.- amyloid β 1-42 and tau proteins are associated with mild cognitive impairment and easily derived from cerebro spinal fluid of a patient (Lewczuk et.al., 2010).
- 5. Biomarkers of Treatment Response:** After administration of drug or treatment, treatment response biomarkers are easily found in individuals system. E.g.- elevated levels of cytokine is associated with antidepressant effects of exercise (Rethrost et.al., 2013)
- 6. Biomarkers of Prognosis:** The prediction of likely course and outcome of an illness is detected by prognostic biomarkers. The expression of such biomarkers enables the clinician to detect the proper dosage for treatment. E.g.- major depressive disorder patients are likely to show more TNF α and IL-6 expression and poor response to antidepressant therapy (Krishnadas and Cavanag, 2012).

VI. BIOMARKERS FOR HEPATIC DISEASES

Liver is the largest internal organ in a human body. It is responsible for majority of metabolism as well as detoxification functions of drug and other diverse environmental chemicals (Klaassen, 2007). Liver cells are frequently exposed to toxicants of significant concentrations which can adversely affect their specific functions. For example- a commonly used analgesic and antipyretic drug in USA is acetaminophen (Hinson et.ai., 2010). This particular drug upon overexposure leads in production of highly reactive hepatotoxic compounds (Lee,2004). Apart from drugs, hepatic cells often encounter toxicity due to metabolic substances, ingested metal, environmental toxicants etc. as well. Hepatic diseases are often termed as Drug induced liver injury (DILI) caused by high intake of oral drugs (Kaplowitz, 2005). A number of biomarkers are associated with DILI. According to FDA guidelines, a combination of four biomarkers is considered as an indicative measure for DILI (FDA, 2009). ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), ALP (Alkaline phosphatase) and TBL (Total Bilirubin) are the four indicative biomarkers used by

clinicians for detection of DILI (Yang et.al., 2014). Apart from these four biomarkers different hepatotoxic diseases can be identified using specific biomarkers. The table below enlists some of the most common hepatotoxic diseases and the biomarkers associated to them.

Sl. No.	Biomarker	Name of disease
	ALT	Hepatocellular necrosis (ALT is most commonly used marker); ALT is also increased due to heart and skeletal muscle injury.
	ALP	Cholestasis (drug induced), Hepatobiliary injury.
	TBL (disease severity indicator)	Cholestasis, Hepatobiliary, Haemolysis
	AST	Hepatocellular necrosis (ASP is less common than ALT), Extra hepatic tissue injury.
	GGT (Gamma-glutamyltransferase)	Cholestasis, Biliary
	Triglyceride clotting time	Failure of bile elimination, severe hepatic injury
	Urobilinogen	Biliary obstruction in liver (the marker is found in urine)
	Ammonia	Liver injury
	Albumin	Chronic liver disease (indicated by decrease in albumin)

Ref: Ozer et.al.,2008

Apart from these conventional biomarkers, via Omics technique more specific biomarkers for each individual hepatic disease are being discovered in recent times. The need of specificity along with the common biomarkers is the driving force acting behind such specific and detailed experiments by the clinicians. The classification of hepatotoxic biomarkers based on the platforms used for omics are broadly-

- Genetics biomarker of hepatotoxicity
- Genomics biomarker of hepatotoxicity
- Proteomics biomarker of hepatotoxicity
- Metabolomics biomarker of hepatotoxicity and
- MicroRNAs as biomarker of hepatotoxicity.

The discovery of such emerging biomarkers is making the diagnosis not only easier for the practitioners but accurate as well. Some of the examples of emerging hepatotoxicity biomarkers are given below in tabular format.

Sl. No.	Biomarker	Disease	Reference
	Glutathione S-transferase P-form	Hepatocellular injury	Fella et al., 2005; Gluckmann et al., 2007
2.	IL-1	Cellular response to tissue damage	Akbay et al., 1999; Lacour et al., 2005

3.	Paraoxanase 1 (Found in kindey, brain and lung as well)	Hepatocellular necrosis	Amacher et al., 2005; Schomaker et al., 2013
4.	Apolipoprotein E (also found in brain and kidney)	Hepatocellular necrosis	Ozer et al., 2008; Andersson et al., 2009; Bell et al., 2012
5.	Glutathione S-transferase alpha (Liver specific)	Hepatocellular necrosis	Giffen et al., 2002
6.	Purine nucleoside phosphorylase (mainly present in Kupffer cells, hepatocytes and endothelial cells of liver)	Hepatocellular necrosis	Amacher et al., 2005; Schomaker et al., 2013
7.	Acylcarnitines	Failure of fatty acid oxidation	Chen et al., 2009; Zhang et al., 2011
8.	5-Oxoproline	Oxidative stress and glutathione status	Kumar et al., 2010; Xiong et al., 2012
9.	miRNA-122	Viral-, alcohol- and chemical-induced liver injury; hepatocarcinoma	Wang et al., 2009; Starkey Lewis et al., 2011; Ding et al., 2012
10.	miR-291a-5p	Chemical-induced liver injury	Yang et al., 2012b
11.	miRNA-192	Chemical-induced liver injury	Wang et al., 2009
12.	Steroids	Oxidative stress and liver damage	Chen et al., 2009; Kumar et al., 2011; Xiong et al., 2012

VII. BIOMARKERS FOR GENETIC DISEASES

The common conception of genetic disorders in a non medical person is often limited with rare, single gene related commonly observed disorders like cystic fibrosis (CS), Hemophilia, Alzheimer's, Phenylketonuria or some forms of cancer (when a family history of the disease has been diagnosed clearly). But in reality, the genetic basis of disorder is a much larger field of concern. Not only genetic constitution of an individual but other factors like environmental effectors, lifestyle of a particular individual, exposure to certain reactive substances, pathogenic infection, exposure to certain biological agents etc. often leads to critical genetic disorders. Genetic diseases are diagnosed based on certain genomic trait evaluation. The evaluation used to include assays to detect genetic variants in the diseased individual, in a particular population. Regulatory agencies (CHMP/ICH/437986/ 2006) has

very recently introduced the application of genomic biomarkers (GB) for detection of genetic diseases. These GBs are ought to reflect the features of 1. Expression of a gene, 2. Function of a gene and 3. Regulation of genes. Such detailed data on the genetic variants make GBs an important tool for disease diagnosis. GB discovery has thus become a core of interest for both academicians and medical based industries. For a long time period, GBs were used only for diagnosis of genetic disorders with single gene mutations like- familial hypercholesterolemia, hyperkalemia, high blood pressure etc. Polygenic origin of diseases lacking Mendelian pattern of transmission are however difficult to detect using GBs as these are often related to complex environmental factors. Multiple GBs are associated with drug response factors and are termed as genetic biomarkers for response. Some of such examples are-

Sl. No.	Biomarker	Disease	Treatment associated
1.	UGT1A1	Colon cancer	Irinotecan therapy
2.	CYP2C9/VKORC1	Anticoagulant treatment	Warfarin dose
3.	HLA-B*5701	Hypersensitivity syndrome	Abacavir
4.	Philadelphia chromosome	Lymphoblastic leukemia	Gleevec
5.	Her2/neu	Breast cancer	Herceptin

Ref: Novelli et.al., 2008

VIII. PRECISION MEDICINE AND BIOMARKERS: AN INSIGHT INTO MODERN HEALTHCARE:

Precision medicine is a cutting edge approach relying heavily on molecular information and tailored therapeutic strategies to devise individualized treatments in healthcare sector. Biomarkers play a pivotal role in steering this Novel branch where they act as an indicator of diagnostic, prognostic and therapeutic responses. In recent years, the use of terms like "precision medicine" and "personalized medicine" has seen a significant uptick, integrating into routine clinical procedures and understanding. Evolution of biomarkers went hand in hand with personalized medicine. In its early manifestations, precision medicine application revolved around tailoring of medical treatment based on individual patient characteristics. To better grasp the idea of personalized medicine, let's consider a few examples. Historically, tackling infectious diseases required pinpointing the responsible organism and then choosing an effective antimicrobial treatment. When it comes to bacterial infections, this approach is well-established, as thoughtful and empirical antibiotic use has been the norm for a long time. However, the introduction of precision medicine in identifying bacteria or viruses at the point-of-care, especially with insights into their potential sensitivities, could be groundbreaking. Such advancements may expedite and refine treatments, minimizing the risk of antimicrobial resistance. (Jameson 2015). Major application of precision medicine came in the field of medical oncology. For example- In lung cancer apart from the routine classification based on histopathology is augmented by EGFR mutation and amplification, CK18 expression, KRAS mutation (De Petris et al. 2011; Adderley, Blackhall, and Lindsay 2019; N. Yan et al. 2022; Bethune et al. 2010). ALK fusion genes are uncommon, comprising less than 5% in Non-small cell lung cancer (Jameson 2015). Tumors with ALK rearrangements don't overlap with those having EGFR or KRAS mutations. This unique scenario epitomizes the concept of 'oncogene dependency,'

where a singular gene product can induce malignancy. These ALK rearrangements are more prevalent in distinct demographics, particularly younger individuals who have minimal or no smoking history. Using targeted treatments like Crizotinib offers a more favorable prognosis for such patients (Chan and Hughes 2015). A multi-disciplinary approach has been made in the field of precision medicine, it has been enriched by genetics, informatics, and imaging, along with other technologies such as proteomics, epigenetics, metabolomics and transcriptomics which are rapidly expanding the scope of Precision medicine (Bravo-Merodio et al. 2021b). A significant milestone in the journey of precision medicine: the Human Genome Project (HGP) from 1990 to 2003, coupled with the HapMap project initiated in 2002. These groundbreaking projects enabled profound insights into fundamental genome functions, particularly in the exploration, detection, and profiling of polymorphisms, known as SNPs. The advent of genomic screening technologies paved the way for matching the appropriate medications with the right individuals, birthing the domain of pharmacogenomics. This area has become an integral pillar of personalized medicine. The FDA has endorsed 51 distinct pharmacogenetic correlations that aid in therapeutic decisions. Warfarin, an anticoagulant used to treat blood clotting, serves as a prime example in this context whose therapeutic dose depends upon CYP2C9, CYP4F2, VKORC1 variants.

- 1. Biomarkers: Bridging the Gap:** In clinical scenarios, biomarkers play a crucial role in evaluating patients, including gauging the likelihood of diseases and initial screening for cancers. These biomarkers can distinguish between benign and malignant growths, as well as differentiate various cancer types. They are pivotal in establishing a diagnosis, forecasting prognosis, and predicting patient responses post-treatment. One of the notable applications of biomarkers is their ability to ascertain an individual's susceptibility to cancer. For instance, in cases where a woman has a pronounced familial history of ovarian cancer, she might opt for genetic tests to check for specific hereditary mutations, like BRCA1. Possessing this mutation elevates her chances of developing both breast and ovarian cancers (Henry and Hayes 2012). Biomarkers often serve as indicative tools for specific treatments. Take, for instance, the KRAS mutation. KRAS operates as a predictive biomarker, given that its somatic mutations correlate with a diminished responsiveness to therapies targeting the epidermal growth factor receptor (EGFR) (Henry and Hayes 2012). In Chronic Myelogenous Leukemia (CML) BCR-ABL fusion which occurred due to chromosomal translocation from Chromosome 22 of BCR gene to chromosome 9 of ABL gene resulted in BCR-ABL fusion protein (Henry and Hayes 2012). In 2001, Imatinib, also recognized by its brand names "Gleevec" or "Glivec" and identified as a BCR-ABL tyrosine kinase inhibitor, transformed the landscape of chronic myeloid leukemia (CML) treatment, earning it the moniker "magic bullet" (Iqbal and Iqbal 2014). Biomarkers also have a pivotal role in gauging the efficacy of chemotherapy. For instance, circulating soluble protein tumor markers like CEA, PSA, CA125, as well as MUC-1 antigens CA15-3 and CA27.29, and CA19-9, are recommended to track the therapeutic response in metastatic cancers of the colorectal, prostate, ovarian, breast, and pancreas, respectively
- 2. Applications in Neurological Disorders:** Alzheimer's disease stands out as one of the most common neurological disorders. This intricate neurodegenerative condition is marked by an escalating decline in cognitive functions, which affects day-to-day activities. Symptoms include significant memory lapses and changes in both spatial and temporal awareness. It's estimated that around 14 million individuals across Europe and the United States are impacted by this ailment (Lewczuk et al. 2020). Hence, specific

biomarkers are necessary for early diagnosis and prognosis along with the medical intervention needed to improve quality of life. Alzheimer's disease is notably characterized by two primary markers: neuritic plaques, which are composed of the Amyloid- β peptide ($A\beta$), and neurofibrillary tangles (NFTs), which are formed from hyperphosphorylated Tau protein (pTau). Four cerebrospinal fluid (CSF) biomarkers commonly referenced in relation to this disease are Amyloid beta 42 ($A\beta_{42}$), the $A\beta_{42}/40$ ratio, Tau protein, and Tau phosphorylated at threonine 181 (pTau181), as detailed in Lewczuk et al. 2020. An observable reduction in CSF $A\beta_{42}$ levels and/or the $A\beta_{42}/40$ ratio, coupled with increased CSF concentrations of Tau and/or pTau, predominantly signify the dual pathophysiological processes of Alzheimer's disease, namely amyloidosis and neurodegeneration. A number of Novel CSF biomarkers have been investigated which are specific for pathologic changes whereas some indicate oxidative damage or inflammation this includes β -site amyloid precursor protein cleaving enzyme 1 (BACE1), Heart-type fatty acid-binding protein (hFABP), Chitinase-3-like protein 1 (YKL-40) Increased in CSF and plasma ,Interferon- γ -induced protein 10 (IP-10), Matrix metalloproteinase-9 and -3 (MMP-9 and MMP-3), Synaptosome-associated protein 25 (SNAP-25), α -Synuclein, TDP-43, Visinin-like protein 1 (VILIP-1) and Neurofilament light (NF-L)(Lewczuk et al. 2020). In therapeutic studies, NfL (Neurofilament protein) has been employed as a biomarker for ALS and is integrated into standard clinical diagnostic practices (Reddy and Abeygunaratne 2022). Parkinson's disease (PD) is a progressively debilitating neurodegenerative disorder caused by the deterioration of dopaminergic neurons in the Substantia Nigra pars Compacta (SNc) and the accumulation of Lewy bodies, which are unusual protein aggregates. This condition impacts over 10 million individuals globally. While environmental factors play a role, the genetic underpinnings of both familial and sporadic PD forms have been deeply researched. Families with monogenic hereditary PD variants often possess mutations in the SNCA (4q22.1, α -synuclein) gene. Notably, frequent mutations associated with PD include those in PARK2 (6q26, Parkin) and PINK1 (1p36.12, PTEN-induced putative kinase 1), which are typically inherited as autosomal dominant traits. In contrast, mutations in DJ1 (1p36.23, Protein Deglycase DJ-1) are seen in autosomal recessive forms.(Strafella et al. 2018). A comprehensive analysis of five GWAS (Genome-Wide Association Studies) highlighted eleven associated loci, which include SNPs from SNCA, LRRK2, GBA (1q22, Glucosidase β), and HLA-DRB5 (6p21.32, Major histocompatibility complex, class II, DR β -5). The varying response to PD medications among individuals can be modulated by particular genetic elements. The pharmacogenomics of PD medications primarily focuses on genes associated with dopaminergic activity, including dopamine receptors (DRD1, DRD2, DRD3), transporters (DAT, SLC22A1/OCT1), and enzymes crucial for dopamine metabolism and breakdown (COMT, MAO-B, DDC). Of the dopamine receptor genes, DRD2 has been the most studied. Research indicates that patients possessing the DRD2 13 and 14 repeat alleles (CA) of an intronic Short-Tandem Repeat (STR) exhibited a diminished risk of LID. In contrast, those with the DRD2 15 repeat allele showed more favorable disease outcomes,hence precision medicine can analyse the overall data and generate an omics profile for a better 360 degrees overview of patient(Strafella et al. 2018) .

- 3. Personalized Treatment: Precision Medicine's Crowning Glory:** It will be really fascinating to imagine a world where medical treatment is as unique as one's fingerprint. Using genomic and molecular information, clinicians can now determine how individuals might respond to a treatment by adopting an error free approach. The current imperative

is a sweeping research initiative that fosters innovation within the realm of precision medicine, conducts meticulous clinical trials, and consequently establishes a foundation of evidence that will steer clinical practices (Collins and Varmus 2015). Precision medicine's nuanced molecular approach towards cancer will complement and refine, rather than supplant, the prevailing successful oncological methodologies related to prevention, diagnostics, certain screening techniques, and efficacious treatments. This will solidify a resilient structure to expedite the incorporation of precision medicine in other domains, with inherited genetic disorders and infectious diseases being at the forefront of these areas

IX. CONCLUSION

Biological markers are the latest diagnostic measure in clinical practices. Due to specificity of expression at each stage both prognosis and diagnosis of complex diseases have become easier with accuracy. Application of 'Omics' in determination of biomarkers is not only specific but a rapid process. Both diagnostic industries and research laboratories are focusing on these techniques for better output. Recent day techniques for precision medicine depend majorly on molecular methods. In this chapter we have elaborately described about the properties of biomarkers, types of biomarkers, list of biomarkers associated to particular diseases, prognostic and diagnostic biomarkers of particular diseases and biomarkers in precision medicine. It is to be concluded that biomarkers due to their accuracy, can be regarded as one of the best diagnostic tool for uni as well as multi-factorial complex diseases. Determination of stage and extent of a complex disease at genetic or protein level makes the diagnosis easier and treatment becomes more specific by the clinicians. More upcoming experiments on this particular field will enable the medical practitioners and researchers with easiness and accuracy of detection and diagnosis.

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