e-ISBN: 978-93-5747-464-1
IIP Proceedings, Volume 2, Book 27, Part 2, Chapter 3

BIOMARKERS

Author

Dr. Suman Doddamani
Assistant professor
Department of Biochemistry
Karnataka institute of medical sciences
Hubli, Karnataka

I. BIOMARKERS

Biomarker is anything that can be measured as an indicator of a biological process. Biomarker is evaluated and measured as an indicator of physiological processes, as a response to pathogenic process or as a pharmacological response to a therapeutic intervention. The biomarker can be produced by the body as a response to a disease. These biomarkers play a pivotal role in various stages of patient management. Even before the diagnosis, biomarkers are used for risk assessment and also for screening. During the process of diagnosis, biomarker can be used for staging and grading of the disease. They also help in selecting the mode of therapy. In the later stage, biomarker can be used to monitor the treatment, can help in guiding the physician to make any addition or deletion of drugs. They also help in monitoring the recurrence of the disease.

1. There are different phases of evaluation of Biomarkers.

- Phase 1 – (pre-exploratory studies) the process involved in this phase are gene selection, gene expressions to differentiate between abnormal and normal samples. The biomarkers which are identified are prioritized based on their predictive value (diagnostic / prognostic/ therapeutic). This would suggest their evolution into clinical use routinely. The specimens used during phase I should be ideally from well-characterized cohorts, or from a trial with active follow ups.
- Phase II – Is a phase characterized by establishing an assay methodology for the estimation of the biomarker. It can be RNA, DNA, proteins or a cell based techniques like ELISA, can use mass spectrometry etc. These assays are validated for reproducibility, sensitivity and specificity.
- Phase III Clinically diagnosed cases are subjected for measuring the levels of biomarker and are analyzed for sensitivity and specificity.
- Phase IV This phase involves prospective cohort, on whom the evaluation of sensitivity and specificities of the test is being carried out. Unlike phase II a positive test result triggers a definitive diagnostic procedure at phase IV stage.
- Phase V The overall benefits and risks of the newer diagnostic test are evaluated on the screened population in phase V

2. Characteristics of an Ideal Biomarker

- It should be safe and the measurement should be easy.
- There should be a proven treatment methodology to modify the biomarker.
- Follow up tests should be relatively of low cost
- The biomarker used for assessment should be consistent across ethnic groups and across gender.

3. Types of Biomarkers

- Diagnostic Biomarkers : These markers are used to confirm the presence of a disease or a medical condition
- Monitoring Biomarker: These are used to assess the presence of the disease to know the extent of a disease, or to evaluate the response of an intervention.

- Response Biomarker: These are used to assess the presence of the disease, to know the extent of a disease, or to evaluate the response of an intervention.
- Predictive Biomarkers: These are used to identify the predictive nature or in other words, to identify the probability of development of a clinical event, after the exposure to an environmental agent
- Prognostic Biomarker: These are used to measure the individuals risk to acquire a disease.
- Safety Biomarker:These are used to predicttoxic adverse events induced by medical intervention like drugs or exposure to environmental agents.

4. Applications of Biomarkers

- They help in assigning predictability for certain diseases
- They can be helpful in identifying precursors for advanced diseases such as blood disorders or cancers
- They play a pivotal role in drug discovery and development process.

II. USES OF BIOMARKERS

Biomarkers can be used in assessment of the exposure (absorbed amount or internal dose) and effects of chemicals and the susceptibility of individuals. Biomarkers may be used to elucidate cause-effect and dose-effect relationships in health risk assessment.The measurement of Biomarkers provides the critical link between chemical exposure, internal dose and health impairment, and are of value in assessment of risk. There is a need to identify and validate those characteristic parameters for each organ system that are indicative of induced dysfunction, clinical toxicity or pathological change, also to establish the specificity and sensitivity of each biomarker and its method of measurement.

1. **Requirement of Biomarkers:** Some chronic diseases, which require the patient to take medicines for years, the diagnosis of such disease become important, especially when there are side effects associated with the treatment. Some diseases like Rheumatoid arthritis, Alzheimer's diseases, usually begin with less symptoms, in such patients the biomarkers may help to know the probability of the patient developing the symptoms.

2. **Biomarkers in drug development:** Throughout the process of drug discovery and development, biomarkers are useful. The aim of drug development will be to produce an effective drug at lower cost. eg- During the development of Gefitinib, epidermal growth factor receptor tyrosine kinase inhibitor (EGRF, TKI).

    - **Biomarkers of cancer:** One of the important use of Biomarkers is in the diagnosis and management of cancer. The questions that can be answered by the biomarkers can been described from Fig 1

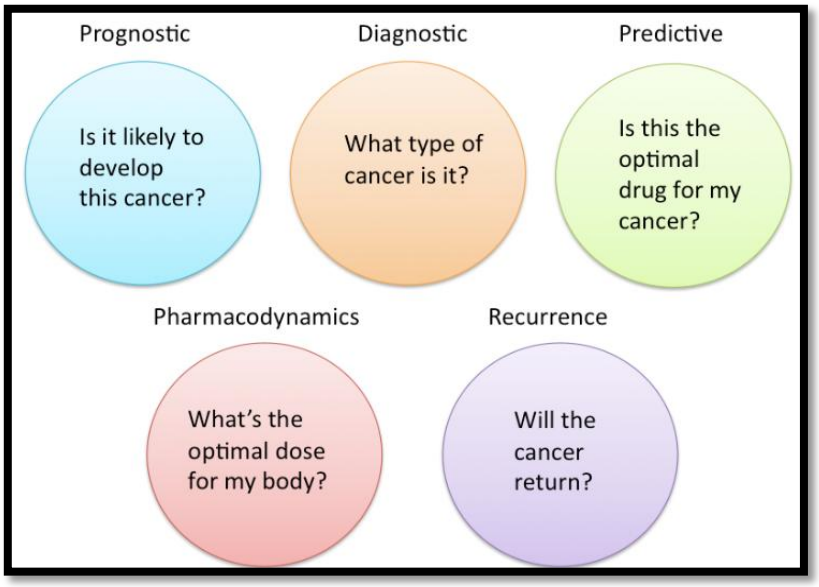

Figure 1: Questions That Can Be Answered By Cancer Biomarkers

Table 1: Biomarkers Used In Various Types Of Cancer

Type of Cancer	Biomarker
Breast	ER/PR (estrogen receptor/progesteron receptor)[1,2]
	Human epidermal growth factor receptor (HER-2/neu)[1,2]
Colorectal	Epidermal Growth Factor Receptor (EGFR)[1,2]
	KRAS[1,3]
	UGT1A1[1,3]
Gastric	HER-2/neu[1]
Gastro Intestinal Stromal Tumors	c-KIT[1,4]
Leukemia/lymphoma	CD20[2,5]
	CD30[1,6]
	FIP1L1-PDGFRalpha[1,7]
	Platelet derived growth factorDGFR[1,8]
	Philadelphia chromosome (BCR/ABL) [1,9,10]
	PML/RAR-alpha[1,11]
	TPMT[1,12]
	UGT1A1[1,13]
Lung	Echinoderm microtubule associated protein-like 4EML4/ALK[14,15]
	EGFR [1,2]
	KRAS [1,2]
Melanoma	BRAF[1, 15]
Pancreas	Elevated levels of leucine, isoleucine and valine[16]
Ovaries	CA-125[17]

3. Biomarkers of cardiac diseases.

Biomarker	Sensitivity and specificity	Approximate peak	Description
Troponin I	Troponin I is one of the specific marker for diagnosis of myocardial infarction. It is a more specific marker than CK-MB [(12)]. The three components of Troponin are Troponin C, Troponin I and Troponin T	18-24 hours	Troponin I even though is a specific marker for myocardial infarction, it is a non enzymatic marker unlike Creatinine kinase (CK-MB). It starts rising 4-10 hours after myocardial infarction, reaches its peak level at 18-24 hours and comes back to normal level by 8-14 days. The normal value of Troponin I is 0 – 0.04 ng/mL.
Creatine Kinase (CK-MB) test	It is relatively less specific marker when compared to Troponin I, it is an enzymatic marker unlike Troponin I.	18–24 hours	Creatine kinase has several isoenzyme forms, CK-MB, CK-BB and CK-MM. among these CK-MB is cardiac specific. It is less specific than Troponin I, But CK-MB has a very good role in assessment of reperfusion. This enzyme starts to rise by3-6 hours, reaches its peak by 18 – 24 hours and comes back to normal by 36 to 72 hours. The normal range of creatinine kinase is 15 – 100 U/L for males and 10 – 80 U/L in females. n
Lactate dehydrogenase (LDH)	LDH is an enzymatic marker. LDH is less specific cardiac marker compared to Troponin I	72 hours	Lactate dehydrogenase is the enzyme required for convertion of pyruvate to lactate. The isozyme found in heart muscle is LDH-1. Normally the levels of LDH-2 is more than LDH-1 which is called flipped pattern. An increased LDH-1/LDH-2 ratio indicates the possibility of Myocardial infarction.

Aspartate transaminase (AST)			This was used earlier. It is a non-specific marker for detecting heart damage
Myoglobin	This biomarker has low specificity for detection of myocardial infarction	2 hours	Myoglobin is one of the not- commonly used marker. The function of Myoglobin is to transport oxygen to the muscles. The increase in the levels of moglobin is seen when muscle tissue is damaged, but it lacks specificity. One of the important advantage of Moglobin is its rapid response.[18)] The rise in CK-MB is seen before any other markers raise. It also has been used in assessment of reperfusion after thrombolysis[(19)]
Ischemia-modified albumin (IMA)	Less specific marker		This biomarker can be measured by albumin cobalt binding (ACB) test. When the myocardial cells undergo ischemia, there is alteration in the N-terminus of albumin. This reduces the affinity of cobalt to albumin. IMA measures ischemia in the blood vessels. Hence it takes very minimal time to obtain the report unlike the other cardiac markers which take hours to obtain the report.
Pro-brain natriuretic peptide			This marker has a role in detection as well as prediction of heart failure. Hence can be used for early detection of structural heart disease.
Glycogen phosphorylase isoenzyme BB		7 hours	Glycogen Phosphorlase-BB is one of the "new cardiac markers"used in early diagnosis of acute coronary syndrome.

			Ischemia leads to conversion of GP-BB into a soluble form, which is released into the blood. A quick rise in blood levels can be seen in unstable angina and myocardial infarction. GP-BB is found to be elevated for upto 3 hours after process of ischemia.

Disadvantages of Biomarkers

- Most of the biomarkers cannot be used as surrogate endpoints to assess the clinical outcomes.
- There are lot of difficulties associated with validation of methods used to measure the biomarkers. They also require validation at different levels
- It is difficult to measure the success of therapeutic intervention, using biomarkers alone.

REFERENCES

[1] Table of Pharmacogenomic Biomarkers in Drug Labels". U.S Food and Drug Administration.
[2] "Tumor Markers Fact Sheet". American Cancer Society.
[3] Heinz-Josef Lenz. Biomarkers in Oncology: Prediction and Prognosis.2012, Springer Science & Business Media.
[4] Gonzalez RS, Carlson G, Page AJ, Cohen C "Gastrointestinal stromal tumor markers in cutaneous melanomas: relationship to prognostic factors and outcome". American Journal of Clinical Pathology. 2011,136 (1): 74-80.
[5] 111Tam CS, Otero-Palacios J, Abruzzo LV, Jorgensen JL, Ferrajoli A, Wierda WG, et al. "Chronic lymphocytic leukaemia CD20 expression is dependent on the genetic subtype: a study of quantitative flow cytometry and fluorescent in-situ hybridization in 510 patients". British Journal of Haematology 2008, 141 (1):36–40.
[6] Zhang M, Yao Z, Patel H, Garmestani K, Zhang Z, Talanov VS, et al. "Effective therapy of murine models of human leukemia and lymphoma with radiolabeled anti-CD30 antibody, HeFi-1". Proceedings of the National Academy of Sciences of the United States of America 2008. 104 (20)8444–8448.
[7] Yamada Y, Sanchez-Aguilera A, Brandt EB, McBride M, Al-Moamen NJ, Finkelman FD, et al. (September 2008). "FIP1L1/PDGFRalpha synergizes with SCF to induce systemic mastocytosis in a murine model of chronic eosinophilic leukemia/hypereosinophilic syndrome". Blood. 112 (6):2500–2507. doi:10.1182/blood-2007-11-126268.
[8] NimerSD. "Myelodysplastic syndromes". Blood. 2008 (10): 4841–4851. doi:10.1182/blood-2007-08-078139.
[9] Ottmann O, Dombret H, Martinelli G, Simonsson B, Guilhot F, Larson RA, et al. "Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or

intolerance to imatinib: interim results of a phase 2 study"2007. Blood. 110 (7): 2309–2315.
[10] Boulos N, Mulder HL, Calabrese CR, Morrison JB, Rehg JE,Relling MV, et al. "Chemotherapeutic agents circumvent emergence of dasatinib-resistant BCR-ABL kinase mutations in a precise mouse model of Philadelphia chromosome-positive acute lymphoblastic leukemia". Blood 2011. 117 (13): 3585–3595. doi:10.1182/blood-2010-08-301267.
[11] O'Connell PA, Madureira PA, Berman JN, Liwski RS, Waisman DM (April 2011). "Regulation of S100A10 by the PML-RAR-α oncoprotein". Blood. 117 (15): 4095–4105. doi:10.1182/blood-2010-07-298851.
[12] Duffy MJ, Crown J. "A personalized approach to cancer treatment: how biomarkers can help". Clinical Chemistry 2008. 54 (11): 1771-1779. doi:10.1373/clinchem.2008.110056.
[13] Ribrag V, Koscielny S, Casasnovas O, Cazeneuve C, Brice P, Morschhauser F, et al. (April 2009). "Pharmacogenetic study in Hodgkin lymphomas reveals the impact of UGT1A1 polymorphisms on patient prognosis". Blood. 113 (14): 3307–3313. doi:10.1182/blood-2008-03-148874.
[14] Li Y, Ye X, Liu J, Zha J, Pei L. "Evaluation of EML4-ALK fusion proteins in non-small cell lung cancer using small molecule inhibitors". Neoplasia 2011. 13 (1): 1–11. doi:10.1593/neo.101120.
[15] Pao W, Girard N "New driver mutations in non-small-cell lung cancer". The Lancet. Oncology2011. 12 (2): 175–180. doi:10.1016/S1470-2045(10)70087-5.
[16] Hewes A. "Promising Method for Detecting Pancreatic Cancer Years Before Traditional Diagnosis". Singularity,2016-04-22.
[17] Gupta D, Lis CG. "Role of CA125 in predicting ovarian cancer survival - a review of the epidemiological literature". Journal of Ovarian Research. 2013.2 (1): 13. doi:10.1186/1757-2215-2-13.
[18] "Use of Cardiac Markers in the Emergency Department: - eMedicine". Retrieved 2009-01-06.
[19] Christenson RH; Ohman EM; Topol EJ; et al. "Assessment of coronary reperfusion after thrombolysis with a model combining myoglobin, creatine kinase-MB, and clinical variables. TAMI-7 Study Group. Thrombolysis and Angioplasty in Myocardial Infarction-7". Circulation. 96 (6): 1776–82. doi:10.1161/01.cir.96.6.1776.

