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REVIEW ARTICLE

Biomarkers: The Curious Tool for Diagnosis, Prognosis and Treatment

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A B S T R A C T

The complication and severity of disease can be reduced if the diagnosis and treatment can be made at early stage. This has led to search of tools called molecular biomarker, which help in early diagnosis of disease, predict future disease progression, and evaluate the response to therapy thus avoiding complications. Biomarkers are being used in both the field of medicine and dentistry for diagnosis, monitoring of therapy outcomes, and drug discovery. In the field of periodontics salivary and GCF biomarkers are being used for detection of active disease state, for monitoring the response to therapy or for measuring the degree of susceptibility to future disease progression. This review highlights about different characteristics of biomarkers and their role in periodontal disease.

Key Words: GCF, Saliva, Therapy Monitoring

Introduction

Biomarkers have been defined by Hulka and colleagues(1990)[1]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 include biological 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] In practice, biomarkers include tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression, or outcome of treatment of disease

Biomarkers are potentially useful along the whole spectrum of the disease process. Before diagnosis, markers could be used for screening and risk assessment. During diagnosis, markers can determine staging, grading, and selection of initial therapy. Later, they can be used to

monitor therapy, select additional therapy, or monitor recurrent diseases.

CLASSIFICATION OF BIOMARKER

Biomarkers can be classified based on different parameters.[3]

Based on their characteristics such as:

1. Imaging biomarkers- (Computed Tomography, Proton Emission Tomography, and Magnetic Resonance Imaging)
2. Molecular biomarkers- Molecular biomarkers can be used to refer to non-imaging biomarkers that have biophysical properties, which allow their measurements in biological samples (example, plasma, serum, cerebrospinal fluid, bronchoalveolar cleavage, and biopsy) include nucleic acids-based biomarkers such as gene mutations or polymorphisms and quantitative gene expression molecules.[4]

Based on genetic and molecular biology methods -

Type 0- Natural history markers: A marker of natural history of a disease and correlates longitudinally with known clinical indices.

Type 1- Drug activity markers: A marker that captures the effect of a therapeutic intervention in accordance with its mechanism of action.

Type 2- Surrogate markers: A marker intended to substitute for a clinical end point; a surrogate end point is expected to predict clinical benefit or lack of benefit on the basis of epidemiology, therapeutic, patho-physiological or other scientific evidence.

Biomarkers based on drug development can be describe as-

Diagnostic biomarkers- provides the means to define a population with a specific disease. (i.e., cardiac troponin for the diagnosis of myocardial infraction.)

Prognostic biomarkers- correlate with outcomes. For example, over

expression of Her-2/neu in breast cancer or EGFR expression in colorectal cancer indicates poor prognoses.

Predictive biomarkers -define populations that might respond more favorably to a particular intervention from an efficacy or safety perspective.[5]

PHASES OF EVALUATION OF BIOMARKERS[6]

Phase 1 refers to preclinical exploratory studies. Biomarkers are discovered through knowledge based gene selection, gene expression profiling or protein profiling to distinguish cancer and normal samples.

Phase II-an assay is established with a clear intended clinical use. The clinical assay could be a protein-, RNA-,DNA- or a cell-based technique, including ELISA, protein profiles

from MS, phenotypic expression profiles, gene arrays, antibody arrays or quantitative PCR. the assays should be evaluated for their clinical performance in terms of 'sensitivity 'and 'specificity' with thresholds determined by the intended clinical use.

Phase III, an investigator evaluates the sensitivity and specificity of the test for the detection of diseases that have yet to be detected clinically.

Phase IV evaluates the sensitivity and specificity of the test on a prospective cohort.

Phase V evaluates the overall benefits and risks of the new diagnostic test on the screened population.

BIOMARKER DISCOVERY USING HIGH-THROUGHPUT TECHNOLOGY PLATFORMS (Table.1)[7] (Fig.1)[8]

Fig 1. *Current technologies and data types used for biomarker discovery in preclinical and clinical research.*

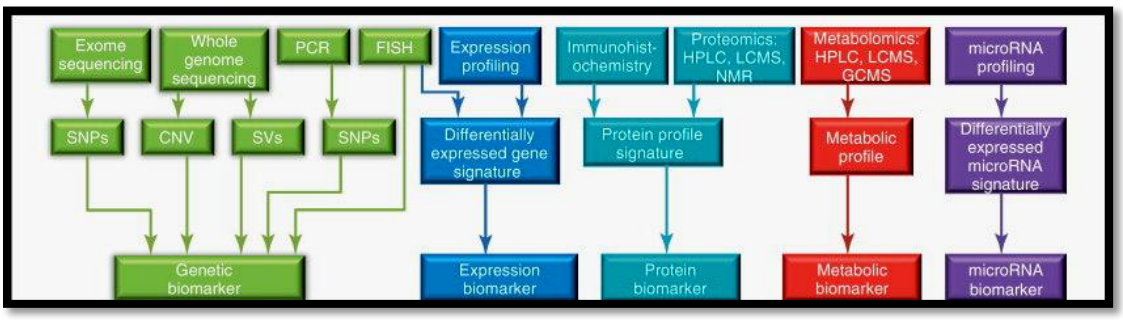


Table 1-High-throughput technologies.

1) Genomics
- **Genome sequencing**
- **Genome variation**
- **Genome annotation**

2) Transcriptomics
- **Microarrays**
- **Gene expression data**

3) Proteomics
- **Y2H method**
- **Mass spectrometry**
- **Protein chips**

4) Metabolomics
- **NMR**
- **Mass spectrometry**

BIOMARKER AS AN EMERGING TOOL[9]:

Biomarker in Diseases (Fig.2)[7]

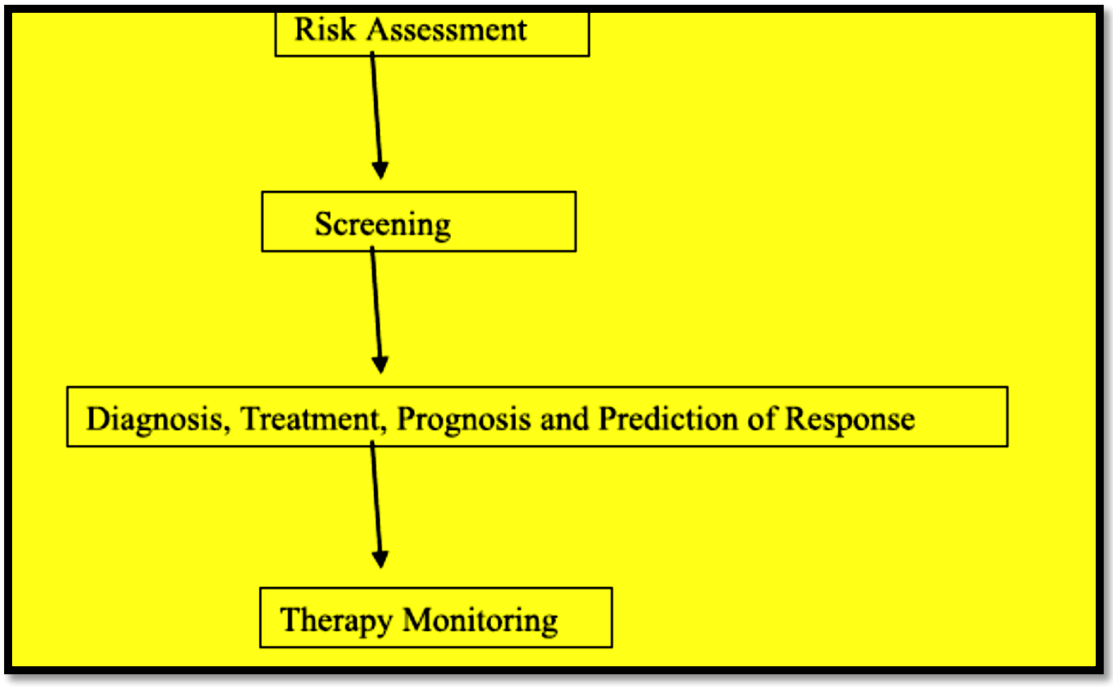


Fig 2. *Schematic representation of the uses of biomarkers across the spectrum of diseases.*

Biomarker in Drug Development:

Biomarkers are useful throughout the drug discovery and development process. They are now becoming more and more integrated into all stages of the development process, ranging from:

- Target discovery
- Evaluation of drug activity
- Understanding mechanisms of action
- Toxicity and safety evaluation
- Internal decision making
- Clinical study design
- Diagnostic tools
- Understanding disease process

ROLE OF BIOMARKERS IN PERIODONTAL DISEASES

Saliva and GCF are fluids easily collected and they contain locally and systemically derived markers of periodontal disease; they may offer the basis for a patient-specific biomarker assessment for periodontitis and other systemic diseases. Due to the noninvasive and simple nature of their collection, analysis of saliva and GCF may be especially beneficial in the determination of current periodontal status and a means of monitoring response to treatment (Table 2[10] and Fig.3[11]lists a sample of compounds obtained by diagnostic screening of saliva or GCF.

Chairside diagnostic kit

Some chair side diagnostic kits have developed that analyses the gingival crevicular fluid (GCF). Since this fluid is derived from periodontal

tissues, evaluating its constituents such as host-derived enzymes, inflammation mediators and extracellular matrix components may provide early signs of alterations. [Table 3] [12,13].

Table 2. Examples of biomarkers of periodontal disease

Category mediator	Examples
Microbial factors	DNA probes or culturing of putative periodontal pathogens (eg, *Porphyromonas gingivalis, Tanerella forsythensis, Treponema denticola*)
Host response factors	IL-1β; TNF-α; aspartate aminotransferase; elastase
Connective tissue breakdown products	Collagen telopeptides; osteocalcin; proteoglycans; fibronection fragments

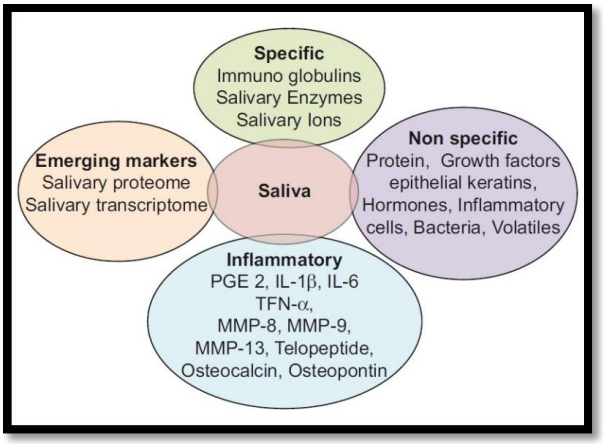
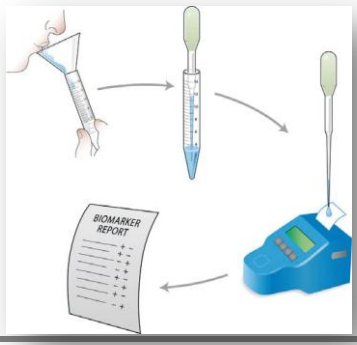


Fig 3. *Biomarkers seen in saliva*

Futuristic chairside diagnostic test based on GCF sampling (Fig.4)[23]

Considering the GCF fluid as a potential analyte for the screening of multiple biomarkers, a rapid, chairside diagnostic tool (represented in the figure as a Micro Analyser) or a "mini-lab" could be used by clinicians for risk assessment and decision making on treatment planning. The advantages of such a tool would be enhanced predictability of clinical outcomes and well-informed patients regarding personalized treatment needs.

Fig 4. Futuristic chairside diagnostic test based on GCF sampling



DISCUSSION

Biomarkers have gained immense scientific and clinical value and interest in the practice of medicine. Biomarkers are potentially useful along the whole spectrum of the disease process. Before diagnosis, markers could be used for screening and risk assessment. During diagnosis, markers can determine staging, grading, and selection of initial therapy. During treatment, they can be used to monitor therapy, select additional therapy, or monitor recurrent diseases[9]. Advances in genomics, proteomics and molecular pathology have generated many candidate biomarkers with potential clinical value[7]. In the field of oral disease diagnosis, there has been a steady growing trend during the last 2 decades to develop tools to monitor periodontitis. From physical measurements such as periodontal probing to sophisticated genetic susceptibility analysis and molecular assays for the detection of biomarkers on the different stages of the disease, substantial improvements have been made on the understanding of the mediators implicated on the initiation and progression of periodontitis. At the same time, this evolutionary process has promoted the discovery of new biomarkers and the development of new therapeutic approaches mainly using host modulation. Moreover, new diagnostic technologies such as nucleic acid and protein microarrays and microfluidics are under development for risk assessment and comprehensive screening of biomarkers. These recent advances are leading to the development of more powerful diagnostic tools for practitioners to optimize their treatment predictability.[10]

CONCLUSION

The biomarkers are emerging as a new and powerful tool in field of both medicine and dentistry for proper screening, diagnosis of disease, evalute prognosis, prediction of disease recurrence and therapeutic monitoring. They are also used for drug development and biomedical research. Various biomarkers present in saliva and GCF seems to be promising for future applications related to diagnosis of periodontal diseases and to prognosticate periodontal treatment outcomes.

KIT	ASSAY
Periocheck[14]	Periocheck has FDA (Food and Drug Administration) approval in the United States. It is reported to measure neutral protease activity within GCF.
Periogard[15]	PerioGard is based on the detection of an enzyme called aspartate aminotransferase (AST). Elevated total AST levels in a 30-second sample have been positively associated with disease-active sites
Prognostik[14]	It detects elevated levels of MMPs in the gingival crevicular fluid such as the elastases. Not Approved by FDA and ADA
Biolise[16]	Aids in detection of elastase
Pocket watch[17]	Detects aspartate aminotransferase through colorimetric detection

TOPAS[15]	**Detects toxins derived from anaerobic metabolism and measures GCF protein level**
MMP dipstick method[18]	Helps in detection of MMPs
Oral Fluid NanoSensor Test[19]	Simultaneous and precise detection of multiple salivary proteins and nucleic acids. It analyzes saliva for the presence of four salivary mRNA biomarkers (SAT, ODZ, IL-8, and IL-1b) and two salivary proteomic biomarkers (thioredoxin and IL-8)
Electronic Taste Chips[20]	Detects multiple biomarkers for early diagnosis of periodontal disease
Integrated Microfluidic	For Oral Diagnostics rapidly

Platform For Oral Diagnostics (IMPOD) [21]	(3–10 min) measures the concentrations of MMP-8 and other biomarkers in small amounts (10 mL) of saliva
Salivary diagnostic and research assay kits (Salimeterics)[22]	Helps in the estimation of cytokines including interleukins, MMPs and so forth and various hormones including cortisol, cortinine, DHEA, testosterone, estradiol, progesterone, estriol in saliva

Table 3. *Chairside diagnostic kit*

REFERENCES

1.Hulka BS. Overview of biological markers. In: Biological markers in epidemiology (Hulka BS, Griffith JD, Wilcosky TC, eds), New York: Oxford University Press, 1990:3–15.

2.Naylor S. Biomarkers: current perspectives and future prospects. *Expert Rev Mol Diagn2003;* 3: 525–529.

3.Pradeep Sahu, Neha Pinkalwar, Ravindra Dhar Dubey, Shweta Paroha, Shilpi Chatterjee and Tanushree Chatterjee: Biomarkers: An Emerging Tool for Diagnosis of a Disease and Drug Development, *Asian J. Res. Pharm. Sci.* 2011; 1(1): 09-16.

4. Gertrude H. Sergievsky Center and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University. New York.10032.

5. U.S. Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products. Rockville, MD: U.S. Food and Drug Administration,U.S. Department of Health and Human Services; March 2004.www.fda.

6.Sullivan Pepe M .Phases of biomarker development for early detection of cancer; *J. Natl. Cancer Inst2001;* 93:1054–1061.

7. Manoj Kumar and Shiv K Sarin. Biomarkers of diseases in medicine, *Current Trends In Sciences* 2009;403-417.

8.Avisek Deyati, ErfanYounesi,Martin Hofmann-Apitius Natalia Novac

Challenges and opportunities for oncology biomarker discovery, *Drug discovery today* 2013; 18 (13-14) :614-624.

9. Richard Mayeux. Biomarkers: Potential Uses and Limitations. *NeuroRx.* 2004; 1(2): 182–188.

10.Mario Taba, Jr, Janet Kinney, Amy S. Kim,and William V. Giannobile, Diagnostic

Biomarkers for Oral and Periodontal Diseases: *Dent Clin North Am*. 2005 July; 49(3): 551–571

11. Priti Basguada Patil and Basgauda Ramesh Patil. Saliva: A diagnostic biomarker of periodontal diseases, *J Indian Soc Periodontol* 2011 ; 15(4): 310–317.

12.CD Dwarakanath, Sheetal Oswal. Relevance of gingival crevice fluid components in assessment of periodontal disease - A critical analysis, *Journal of Indian Society of Periodontology 2010; 14 (4):282-286.*

13.Vishakha Grover, Anoop Kapoor, Ranjan Malhotra and Gagandeep Kaur. Clinical Relevance of the Advanced Microbiologic and Biochemical Investigations in Periodontal Diagnosis: A Critical Analysis , *Journal of Oral Diseases DiseaVolume*,2014 (2014), Article ID 785615, 11 pages

14. Page RC. Host response tests for diagnosing periodontal disease. *J Periodontol* 1992;63:356-66.

15. Eley BM, Cox SW. Advances in periodontal diagnosis, Commercial diagnostic tests based on GCF proteolytic and hydrolytic enzyme levels. *Br Dent J* 1998;184:373-6.

16.Hermann JM, Gonzales JR, Bodeker RH, Vonholdt J, Meyle J. Microassay for the detection of elastase activity in the gingival crevice. *J Clin Periodontol* 2001;28:31-7.

17. K. Shimada, T. Mizuno, K. Ohshio, M. Kamaga, S. Murai, and K. Ito, "Analysis of aspartate aminotransferase in gingival crevicular fluid assessed by using PocketWatch: a longitudinal study with initial therapy," *Journal of Clinical Periodontology2000*; 27 (11): 819–823.

18. Mantyla P, Stenman M, Kinane DF, Tikanoja S, Luoto H, Salo T, *et al*. Gingival crevicular fluid collagenase 2 (MMP-8)test strick for chair side monitoring of periodontitis. *J Periodont Res* 2003;38:436-9

19.UCLA Collaborative Oral Fluids Diagnostic Research Center, 2006, http://hspp.ucla.edu/

20. N. Christodoulides, S. Mohanty, C. S. Miller et al., "Application of microchip assay system for the measurement of C-reactive protein in human saliva, *Lab Chip.* 2005 Mar;5(3):261-9.

21. E. Herr, A. V. Hatch, D. J. Throckmorton et al., "Microfluidic immunoassays as rapid saliva-based clinical diagnostics," *Proceedings of the National Academy of Sciences of the United States of America 2007*;104(13): 5268–5273.

22. Salivary research and diagnostic kits," https://www.salimetrics.com/assay-kits.

23. William V. Giannobile, ThomasBeikler, Janet S.kinney,Christoph A, Thiagomorelli& David T. Wong, Saliva as a diagnostic tool for periodontal disease: current state and future

directions: *Periodontology 2000* 2009; 50: 52–64

24. Schipper R, Loof A, de Groot J, Harthoorn L, Dransfield E, van Heerde W. SELDI-TOF-MS of saliva: Methodology and pre-treatment effects. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007;847:45–53.

25.Hu S, Arellano M, Boontheung P, Wang J, Zhou H, Jiang J, et al. Salivary proteomics for oral cancer biomarker discovery. *Clin Cancer Res*. 2008;14:6246–52.

26.. Li Y, St John MA, Zhou X, Kim Y, Sinha U, Jordan RC, et al. Salivary transcriptome diagnostics for oral cancer detection. *Clin Cancer Res*. 2004;10:8442–50.

27. Hu S, Wang J, Meijer J, Ieong S, Xie Y, Yu T, et al. Salivary proteomic and genomic biomarkers for primary Sjogren's syndrome. *Arthritis Rheum*. 2007;56:3588–600.

28. Zia A , Khan S , Bey A , Gupta ND , Mukhtar-Un-Nisar S .Oral biomarkers in the diagnosis and progression of periodontal diseases ,*Biology and Medicine* 2011; 3(2) Special Issue: 45-52.

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