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# Role of biomarkers in veterinary medicine: A mini-review

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**Abstract**
Biomarkers hold immense promise in revolutionizing various aspects of healthcare. Biomarkers are not limited to human medicine but also play a crucial role in veterinary medicine. They serve as crucial indicators reflecting physiological, pathological, or pharmacological responses to therapeutic interventions. Biomarkers are likely to play a significant role, especially in the field of personalized medicine. As the understanding of the genetic and molecular basis of diseases continues to grow, there's a heightened focus on pinpointing the biomarkers that are associated with certain diseases or conditions. Moreover, biomarkers hold immense promise in drug development. By identifying specific biomarkers that are associated with a disease, researchers can develop drugs and therapies that target those biomarkers, leading to more effective treatments with fewer side effects. Advancements in technology, such as genomics, proteomics, and metabolomics, are also expected to play a significant role in the future of biomarkers. These technologies allow the identification and analysis of large amounts of biological data, which can help to identify new biomarkers and improve our understanding of disease mechanisms.

**Keywords:** Animal diseases, biomarkers, genomics, proteomics, and metabolomics

## Introduction
The use of biomarkers has a significant role to play in advancing veterinary medicine. These biological indicators provide valuable insights into the health status of animals, enabling quicker and more accurate diagnoses, as well as effective monitoring of disease progression, in therapy and management to carter numerous health conditions in animals (Michael and Ball, 2010) [25]. This, in turn, leads to improved animal welfare and productivity. The phrase 'biomarker' is a condensed version that first appeared in the literature in the late 1960s and by the 1990s it became widely used (Myers *et al.*, 2017) [28]. Biomarkers are biological molecules, mostly proteins, that are present in cells, tissues, and body fluids like blood, urine, faeces and exhaled air that can be measured as markers of pathological and physiological situations. A biomarker should ideally be simple and effective in determining the disease's onset and tracking its development (Mobasheri and Cassidy, 2010) [27]. As per the Biomarker Working Group of the National Institute of Health, a Biomarker is defined as a characteristic that can be measured and evaluated as an indicator or predictor of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Eckersall, 2019) [10]. Biomarkers can be classified into various types based on their source or material for measurement, including molecular biomarkers (e.g., DNA, proteins, metabolites), histologic biomarkers (used for grading and staging of neoplasia), and physiologic biomarkers (e.g., blood pressure, heart rate, body temperature) (Perera *et al.*, 2022) [31]. As far as clinical applications are concerned, biomarkers are essential in characterizing baseline health, monitoring disease progression, and assessing the response to treatment in veterinary patient care, clinical research, and therapeutic development. In the context of cancer, a biomarker is defined as a biological molecule found in blood, other body fluids, or tissues that indicates a normal or abnormal process, condition, or disease (Henry, 2010) [17].

In clinical trials, biomarkers can serve as surrogate endpoints, which are biomarkers used to predict the clinical benefit of a therapeutic intervention based on scientific evidence, including epidemiologic, therapeutic, and pathophysiologic data (Aronson *et al*., 2017) [2].

**Characteristics of an ideal biomarker**

The provided points outline several key characteristics and considerations that are important when evaluating and selecting biomarkers for use in veterinary medicine. The following criteria help ensure that biomarkers are effective and reliable for various diagnostic and prognostic purposes (Califf, 2018) [7].

a. **Safety and Efficiency**: Biomarkers should be safe to work with and easy to assay. They should also be cost-efficient and provide rapid results with high precision. This ensures that they are practical and feasible for routine veterinary use.
b. **Accessibility**: Biomarkers should be easily obtainable from readily available sources, such as serum, urine, blood, or serum. This accessibility simplifies the process of sample collection and analysis.
c. **Sensitivity and Half-life**: Biomarkers should exhibit high sensitivity, allowing for early diagnosis. Additionally, they should have a long half-life, which enables their use in late-stage disease diagnosis. Importantly, there should be minimal overlap in values between diseased patients and healthy controls, ensuring accurate differentiation.
d. **Specificity:** Biomarkers should have high specificity, meaning they are significantly regulated in diseased samples and remain unaffected by comorbid conditions. This specificity ensures that the biomarkers are truly indicative of the target disease.
e. **Modifiability with Treatment:** Biomarker levels should be modifiable with treatment. This means that changes in biomarker levels can reflect the response to therapeutic interventions, making them valuable for monitoring treatment efficacy.
f. **Prognostic Value:** Biomarkers should be useful in predicting the prognosis of the disease. They should aid in risk stratification, helping veterinarians make informed decisions about the course of treatment.
g. **Biological Plausibility:** Biomarkers should have a clear cause-and-effect relationship with the underlying disease mechanism. This provides insight into the disease process and helps researchers and veterinarians better understand the condition.
h. **Establishment of Reference Ranges:** To be practical and effective, biomarkers should have established reference ranges and cut-off values for each species, breed, age, and gender. This customization ensures that biomarker assessments are relevant to specific populations.

It's important to note that while these characteristics represent ideal criteria for biomarkers, not all biomarkers will m*eet al*l of these requirements. The choice of biomarkers depends on the specific disease or condition being addressed and the available scientific evidence regarding the biomarker's performance in a particular context (Bennett, 2011; Baisan *et al.*, 2016) [4, 3].

**Advantages of biomarkers**

Biomarkers offer various advantages in different fields of veterinary medicine:

a. Clinical biomarkers, which are simpler and less expensive to measure, provide a cost-effective means of assessing health status or disease presence. This cost-effectiveness can be particularly important in clinical practice and research.
b. Incorporating biomarkers in clinical trials can streamline the research process. By using biomarkers as surrogate endpoints, researchers can potentially reduce the duration of clinical trials and require fewer study subjects. This not only saves time but can also reduce the cost of clinical research.
c. In some cases, the measurement of clinical endpoints, especially in clinical trials, can pose ethical dilemmas or challenges. Biomarkers can help avoid these ethical problems by providing alternative, less invasive ways to assess treatment efficacy or disease progression (Aronson *et al*, 2017) [2].
d. Biomarkers can often detect diseases or health issues at an early stage, allowing for timely intervention and improved treatment outcomes. For example, monitoring metabolic biomarkers in dairy cows can help identify periparturient disease states early, enabling prompt management and reducing economic losses in the dairy industry.
e. Biomarkers can enable personalized or precision medicine approaches by tailoring treatments to an individual's specific biomarker profile. This can lead to more effective and targeted therapies.
f. Biomarkers can enhance our understanding of disease pathogenesis and transmission. They can provide insights into the underlying mechanisms of diseases, which can be valuable for both research and clinical management.
g. In cases such as plant poisoning in livestock, biomarkers can be used to identify the presence and concentration of toxins in the environment and affected animals. This information can guide targeted interventions to prevent further harm.
h. Biomarkers play a crucial role in the diagnosis of infectious diseases, both in human and veterinary medicine. They can aid in early detection and monitoring of infections, contributing to better disease management and prevention.
i. Using biomarkers in veterinary medicine, such as in dairy cow health monitoring, can lead to economic benefits by reducing treatment costs, improving productivity, and minimizing losses.
j. Biomarkers can identify subclinical conditions, which may not exhibit overt clinical symptoms but can have significant impacts on health and productivity. This early detection allows for proactive management (Green, 2023) [12].

In summary, biomarkers offer a range of advantages, from simplifying diagnostics to improving the efficiency of clinical trials and enhancing our understanding of diseases. For example, Periparturient disease states are conditions that occur in dairy cows around the time of calving. These conditions, including metritis, mastitis, and laminitis, can have a significant impact on the health and productivity of dairy cows and can result in significant economic losses for the dairy industry. This condition can lead to decreased milk production, delayed conception, and increased risk of culling altering milk composition, reducing reproductive performance and increasing treatment costs (Hailemariam, 2014) [13]. Monitoring certain metabolic biomarkers in cows can help

identify and potentially prevent health issues. Biomarkers like prepartum NEFA (non-esterified fatty acids) and postpartum BHBA (beta-hydroxybutyrate) levels are associated with the development of clinical disease in cows. Ketone bodies in milk could indicate subclinical ketosis at an early stage (Piechotta *et al*., 2012).

**Classification of Biomarkers**

Based on clinical use or application, biomarkers are classified as monitoring biomarkers, diagnostic biomarkers, pharmacodynamics biomarkers, predictive biomarkers, prognostic biomarkers, susceptible or risk biomarkers, and safety biomarkers (Perera, *et al*., 2022) [31].

**Diagnostic biomarkers:** The biomarkers of this category are used to confirm the presence of a disease or subtype of disease (FDA-NIH, 2016) [11]. Cardiac troponin (cTn) and Brain Natriuretic Peptide (BNP) are the diagnostic as well as prognostic biomarkers of myocardial injury and myocardial stress respectively. Cardiac troponin (cTn) is the most common cardiomyocyte injury-specific leakage marker (Polizopoulou, 2017) [32]. Although troponin levels are determined by human ELISA due to the homology of proteins between species, two veterinary tests are also available for the estimation of cTnI (Baisan *et al.,* 2016) [3]. A novel Silicon nanowire-field effect transistor (SiNW-FET) has been fabricated for the very rapid detection of cTnI having high specificity and sensitivity with a detection limit (Chang *et al*., 2020) [7]. Cardiac troponin levels (cTnI) in blood increase above the normal level proportionally to the degree of myocardial injury in conditions like Myocardial Infarction (MI), Mitral Valve Disease (MVD), congenital heart disease (patent ductus arteriosus, subaortic stenosis etc), pericardial effusion, endocarditis, cardiomyopathy (hypertrophic, dilated), arrhythmias, canine heartworm disease and non-cardiac conditions that cause cardiac insult including chest trauma, Gatro-dilatation-volvulus, babesiosis/ ehrlichiosis, pyometra/sepsis, Addison's disease, Cushing syndrome, renal failure, epilepsy, neoplasia, and hypoxia (Polizopoulou, 2017) [32]. Another diagnostic, risk and prognostic biomarker is Brain natriuretic peptide (BNP)-a is a hormone found in both atrial and ventricular myocardium, but in higher concentration in the latter that controls body fluid homeostasis through natriuretic and diuretic effects by antagonizing Renin-angiotensin-aldosterone mechanism (Baisan, *et al.,* 2016) [3]. Both BNP and NT-proBNP are functional markers of increased myocardial stress that protect the cardiovascular system from volume and pressure overload (Polizopoulou, 2017) [32]. NT-proBNP concentrations are detected by sandwich enzyme immunoassay tests (ELISA). NT-proBNP is a useful indicator of asymptomatic, acute and subacute Myocardial Infarction, arrhythmogenic right ventricular myocardiopathy, congestive heart failure (CHF), pulmonary hypertension, systemic hypertension and also distinguishes between cardiac and non-cardiac dyspnea (Baisan *et al.,* 2016) [3].

**Monitoring biomarkers**: These biomarkers are measured at different time points for assessing the presence, status or extent of disease (FDA-NIH, 2016) [11]. Creatinine, urea and specific gravity are the monitoring biomarkers used in veterinary medicine to monitor acute and chronic renal disease (Cobrin *et al*., 2013) [8]. However, serum creatinine is the primary practical biomarker used in monitoring and grading of acute renal injury (AKI) and staging of chronic kidney disease (CKD) aided by other parameters like degree of azotemia, urine output and proteinuria. Creatinine is measured by chemical and enzymatic methods on an automated analyzer, high-performance liquid chromatography (HPLC), and isotope dilution-mass spectrometry (IDMS). Although creatinine is a practical primary marker for monitoring renal function and GFR indirectly, it has its limitations of being poor sensitivity to early disease and non-renal influences (Hall *et al*., 2015; Sargent *et al.,* 2020) [15, 34]. To overcome the problem a novel endogenous monitoring renal biomarker is devised, Symmetric dimethylarginine (SDMA amino acid arginine) that is produced by all nucleated cells at a constant rate in a body is considered a more sensitive (as compared to serum creatinine) and early marker of declining GFR in animals (Hokamp and Nabity, 2016) [19]. The sensitivity of SDMA as compared to Scr for the early detection of CKD has been evaluated by number of studies which suggest that SDMA detects a decrease in GFR before serum creatinine based on established reference limits (Hall *et al*., 2016) [15].

**Pharmacodynamics biomarker**: These types of biomarkers are used to show that a biological response occurred in an individual exposed to a medical product or an environmental agent (FDA-NIA, 2016) [11]. Pharmacodynamics biomarkers are molecular indicators of drug effect on the target in an organism and are extraordinarily useful both in clinical practice and early therapeutic development. For example, cyclosporine is a potent immunosuppressive calcineurin inhibitor that inactivates T-cells of the immune system and is currently being used to treat a spectrum of inflammatory and immune-mediated diseases. This drug (cyclosporine) exerts its effects by binding to intracellular cyclophilins. Subsequently, this leads to the downregulation of cytokine gene expression, most notably interleukin 2 (IL-2). Decreased IL-2 expression leads to inhibition of proliferation and activation of T cells and blunting of the immune response. Other cytokines similarly affected by cyclosporine include IL-4, interferon-gamma (INF-y), and tumour necrosis factor-alpha (TNF-α). Pharmacodynamic biomarkers**, l**ike activated T-cell expression of IL-2, IL-4, and IFN-γ are investigated via flow cytometry and through pharmacodynamic monitoring and help in optimizing and individualizing therapy (Mackin, 2013) [22].

**Prognostic biomarkers:** these biomarkers identify the likelihood of a clinical event (disease recurrence, progression and overall survival) in patients diagnosed with a disease without the involvement of therapy (FDA-NIH, 2016). For example, Thymidine kinase 1 (TK1) is a diagnostic and prognostic liquid biopsy (blood) biomarker located in the cytosol. In dogs, suffering from lymphomas and myeloid leukaemia activity of TK1 is increased in blood as measured by radio-enzyme assay or ELISA and usually, its activity gets elevated with tumour stage and an increase in activity above 30U/L is associated with decreased overall survival time (1.5 months) (Colombe *et al.,* 2022) [9].

**Predictive biomarkers**: These include markers that identify patients more likely to experience an effect (positive or negative) after exposure to a therapeutic intervention or an environmental agent (FDA-NIH, 2016) [11]. Like, TK1 mentioned above is a predictive biomarker as it decreases significantly in dogs with lymphomas and leukaemias undergoing chemotherapy with partial or complete response,

and up to physiological values and remains significantly higher in cases of relapse or no response to treatment (Colombe *et al*., 2022) [9] and (Califf, 2018) [7].

**Susceptibility or risk biomarkers**: This biomarker indicates the potential for developing a disease in an individual not currently presenting clinically apparent disease (FDA-NIH, 2016) [11]. The main utility of risk biomarkers in clinical practice is to standardize preventive strategies. One of the common examples is Low-density lipoprotein (LDL), sometimes called bad cholesterol, which is the primary carrier of cholesterol to the peripheral tissues and a risk and prognostic biomarker. Patients with elevated LDL cholesterol are at high risk of developing atherosclerosis, coronary artery disease, death, stroke, or myocardial infarction (Califf, 2018) [7].

**Safety biomarkers:** These markers are used to predict toxic adverse events induced by the drug, medical intervention or environmental agent exposure (FDA-NIH, 2016) [11]. Various markers of liver toxicity include alanine Phosphatase. 5'-Nucleotidase, Gamma Glutamyl Transpeptidase, total serum Bile Acids and Plasma Bilirubin indicating Cholestatic Injury; Aspartate Amino Transferase, Lactate Dehydrogenase, Alanine Amino Transferase, Ornithine carbamyl transferase, Alanine aminotransferase indicating Cytotoxic injury etc. Markers of renal toxicity include serum indicators like blood urea nitrogen, creatinine and urine indicators like urinary proteins- tubular (Low MW) or Glomerular (High MW) and urinary glucose, and urinary brush border enzymes (AST, ALP, GGT). Hematology, safety markers include CBC, peripheral blood components, and bone marrow (primary target). Bone safety biomarkers include serum calcium and inorganic phosphates. Basic metabolic safety biomarkers include blood glucose, triglycerides, low-density lipoprotein, high-density lipoprotein etc. Other specific safety biomarkers include thyroid stimulating hormone, thyroxine, cardiac troponin(cTn), methemoglobin etc (Schomaker *et al*., 2019) [35].

**Genomics:** Genomics is the systematic study (including structure, function, evolution, mapping, and editing) of the genome of an organism (Horgan *et al*., 2011) [20]. Genetic heritage has a prominent influence over the health and sickness of an organism, therefore it is important to recognize the mutations and variations that distinguish between health and sickness (Manzoni *et al*., 2018) [23]. Also, response to the treatment and risk of illness is influenced by genetic variation. A whole-genome association study (WGAS) is a research approach to identify a genomic-wide set of genomic variants in different individuals that are associated with a risk for a disease or trait compared to individuals who do not have a disease or trait of interest (Perera *et al*., 2022) [31]. WGAS has enabled the recognition of genetic variants that contribute to the detection of pharmacogenetic markers (Williams *et al*., 2008, Verschuren *et al*. 2012) [36, 37] as well as the pathophysiology of complex genetic diseases (Pandey, 2010). Biomarkers based on DNA Single Nucleotide Polymorphism (SNP), deletions, insertions, Short Tandem Repeats (STRs) and other DNA sequence variations are examples of germline biomarkers. DNA methylation biomarkers compared to expression-based indicators have the advantage of being easily amplifiable and detectable by Polymerase chain reaction (PCR) and can be identified in saliva, urine, sperm and faeces (Herman *et al*., 1996) [18]. Many commercially available kits of DNA biomarkers are available now. In the field of veterinary medicine numerous genetic biomarkers have been discovered which include biomarkers for Familial Dilated Cardiomyopathy inherited as an autosomal dominant trait in Doberman Pinscher dogs detected via PCR, Sequencing (Meurs *et al*., 2007) [24]; Lavender Foal Syndrome with a frameshift mutation in the MYO5A gene in Arabian foal detected by PCR, Sequencing, and genotyping (Brooks *et al*., 2010) [6]; Bovine respiratory disease complex with common genomic regions associated with susceptibility of disease detected via GWAS analysis-SNP identification-qPCR in Holestian calves (Neibergs *et al*., 2014) [29]; Canine Mast Cell Tumor with GNAI2 gene mutation detected via SNP-PCR, Illumina 170K canine HD SNP arrays (Arendt *et al*., 2015) [1].

**Transcriptomics:** The transcriptome is the full range of messenger RNA in a cell or organism and is the initial product of genome expression and the template for protein synthesis in a process called translation (Horgan *et al*., 2011) [20].

## Conclusion

The future of biomarkers is promising, as advances in technology and medical research continue to uncover new ways to detect and utilize these markers. Numerous exciting breakthroughs are anticipated in the coming years within this field. Incorporating biomarkers into veterinary practice has the potential to revolutionize the field by providing faster and more accurate methods for diagnosing and managing diseases in animals. This, in turn, contributes to better animal welfare and public health outcomes.

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